

TITLE OF THE INVENTION

MU-CONOPEPTIDES

CROSS-REFERENCE TO RELATED APPLICATIONS

5 [0001] The present application claims benefit under 35 USC §119(e) to U.S. provisional patent applications Serial No. 60/219,619 filed on 21 July 2000, Serial No. 60/245,157 filed on 3 November 2000, Serial No. 60/264,319 filed on 29 January 2001 and Serial No. 60/277,270 filed on 21 March 2001. Each of these applications is incorporated herein by reference.

10 [0002] This invention was made with Government support under Grant No. P01 GM48677 awarded by the National Institute of General Medical Sciences, National Institutes of Health, Bethesda, Maryland. The United States Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

20 [0003] The present invention is to μ -conopeptides, derivatives or pharmaceutically acceptable salts thereof. The present invention is further directed to the use of this peptide, derivatives thereof and pharmaceutically acceptable salts thereof for the treatment of disorders associated with voltage-gated sodium channels. Thus, the μ -conopeptides or derivatives are useful as neuromuscular blocking agents, local anesthetic agents, analgesic agents and neuroprotective agents. The μ -conopeptides are also useful for treating neuromuscular disorders. The invention is further directed to nucleic acid sequences encoding the μ -conopeptides and encoding propeptides, as well as the propeptides.

25 [0004] The publications and other materials used herein to illuminate the background of the invention, and in particular, cases to provide additional details respecting the practice, are incorporated by reference, and for convenience are referenced in the following text by author and date and are listed alphabetically by author in the appended bibliography.

30 [0005] *Conus* is a genus of predatory marine gastropods (snails) which envenomate their prey. Venomous cone snails use a highly developed projectile apparatus to deliver their cocktail of toxic conotoxins into their prey. In fish-eating species such as *Conus magus* the cone detects the presence of the fish using chemosensors in its siphon and when close enough extends its proboscis and fires a hollow harpoon-like tooth containing venom into the fish. This immobilizes the fish and enables the cone snail to wind it into its mouth via an attached filament. For general information on *Conus* and their venom see the website address

http://grimwade.biochem.unimelb.edu.au/cone/referenc.html. Prey capture is accomplished through a sophisticated arsenal of peptides which target specific ion channel and receptor subtypes. Each *Conus* species venom appears to contain a unique set of 50-200 peptides. The composition of the venom differs greatly between species and between individual snails within each species, each optimally evolved to paralyse its prey. The active components of the venom are small peptides toxins, typically 10-40 amino acid residues in length and are typically highly constrained peptides due to their high density of disulphide bonds.

[0006] The venoms consist of a large number of different peptide components that when separated exhibit a range of biological activities: when injected into mice they elicit a range of physiological responses from shaking to depression. The paralytic components of the venom that have been the focus of recent investigation are the α -, ω - and μ -conotoxins. All of these conotoxins act by preventing neuronal communication, but each targets a different aspect of the process to achieve this. The α -conotoxins target nicotinic ligand gated channels, the μ -conotoxins target the voltage-gated sodium channels and the ω -conotoxins target the voltage-gated calcium channels (Olivera et al., 1985; Olivera et al., 1990). For example a linkage has been established between α -, α A- & ϕ -conotoxins and the nicotinic ligand-gated ion channel; ω -conotoxins and the voltage-gated calcium channel; μ -conotoxins and the voltage-gated sodium channel; δ -conotoxins and the voltage-gated sodium channel; κ -conotoxins and the voltage-gated potassium channel; conantokins and the ligand-gated glutamate (NMDA) channel.

[0007] However, the structure and function of only a small minority of these peptides have been determined to date. For peptides where function has been determined, three classes of targets have been elucidated: voltage-gated ion channels; ligand-gated ion channels, and G-protein-linked receptors.

[0008] *Conus* peptides which target voltage-gated ion channels include those that delay the inactivation of sodium channels, as well as blockers specific for sodium channels, calcium channels and potassium channels. Peptides that target ligand-gated ion channels include antagonists of NMDA and serotonin receptors, as well as competitive and noncompetitive nicotinic receptor antagonists. Peptides which act on G-protein receptors include neurotensin and vasopressin receptor agonists. The unprecedented pharmaceutical selectivity of conotoxins is at least in part defined by a specific disulfide bond frameworks combined with hypervariable amino acids within disulfide loops (for a review see McIntosh et al., 1998).

[0009] There are drugs used in the treatment of pain, which are known in the literature and to the skilled artisan. See, for example, Merck Manual, 16th Ed. (1992). However, there is a demand for more active analgesic agents with diminished side effects and toxicity and which are non-addictive. The ideal analgesic would reduce the awareness of pain, produce analgesia over a wide range of pain types, act satisfactorily whether given orally or parenterally, produce minimal or no side effects, be free from tendency to produce tolerance and drug dependence.

[0010] Due to the high potency and exquisite selectivity of the conopeptides, several are in various stages of clinical development for treatment of human disorders. For example, two *Conus* peptides are being developed for the treatment of pain. The most advanced is ω -conotoxin MVIIA (ziconotide), an N-type calcium channel blocker (see Heading, C., 1999; U.S. Patent No. 5,859,186). ω -Conotoxin MVIIA, isolated from *Conus magus*, is approximately 1000 times more potent than morphine, yet does not produce the tolerance or addictive properties of opiates. ω -Conotoxin MVIIA has completed Phase III (final stages) of human clinical trials and has been approved as a therapeutic agent. ω -Conotoxin MVIIA is introduced into human patients by means of an implantable, programmable pump with a catheter threaded into the intrathecal space. Preclinical testing for use in post-surgical pain is being carried out on another *Conus* peptide, contulakin-G, isolated from *Conus geographus* (Craig et al. 1999). Contulakin-G is a 16 amino acid O-linked glycopeptide whose C-terminus resembles neuropeptid Y. It is an agonist of neuropeptid Y receptors, but appears significantly more potent than neuropeptid Y in inhibiting pain in *in vivo* assays.

[0011] In view of a large number of biologically active substances in *Conus* species it is desirable to further characterize them and to identify peptides capable of treating disorders involving voltage gated ion channels, such as stroke and pain. Surprisingly, and in accordance with this invention, Applicants have discovered novel conotoxins that can be useful for the treatment of disorders involving voltage gated ion channels and could address a long felt need for a safe and effective treatment.

SUMMARY OF THE INVENTION

[0012] The present invention is to μ -conopeptides, derivatives or pharmaceutically acceptable salts thereof. The present invention is further directed to the use of this peptide, derivatives thereof and pharmaceutically acceptable salts thereof for the treatment of disorders associated with voltage-gated sodium channels. Thus, the μ -conopeptides or derivatives are

useful as neuromuscular blocking agents, local anesthetic agents, analgesic agents and neuroprotective agents. The μ -conopeptides are also useful for treating neuromuscular disorders. The invention is further directed to nucleic acid sequences encoding the μ -conopeptides and encoding propeptides, as well as the propeptides.

5 [0013] More specifically, the present invention is directed to μ -conopeptides, having the amino acid sequences set forth in Tables 1 and 2 below.

[0014] The present invention is also directed to derivatives or pharmaceutically acceptable salts of the μ -conopeptides or the derivatives. Examples of derivatives include peptides in which the Arg residues may be substituted by Lys, ornithine, homoarginine, nor-Lys,
10 N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any synthetic basic amino acid; the Lys residues may be substituted by Arg, ornithine, homoarginine, nor-Lys, or any synthetic basic amino acid; the Tyr residues may be substituted with meta-Tyr, ortho-Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any synthetic hydroxy containing amino acid; the Ser residues may be substituted with Thr or any synthetic hydroxylated amino acid; the Thr residues may be substituted with Ser or any synthetic hydroxylated amino acid; the Phe residues may be substituted with any synthetic aromatic amino acid; the Trp residues may be substituted with Trp (D), neo-Trp, halo-Trp (D or L) or any aromatic synthetic amino acid; and the Asn, Ser, Thr or Hyp residues may be glycosylated. The halogen may be iodo, chloro, fluoro or bromo; preferably iodo for halogen substituted-Tyr and bromo for halogen-substituted
20 Trp. The Tyr residues may also be substituted with the 3-hydroxyl or 2-hydroxyl isomers (meta-Tyr or ortho-Tyr, respectively) and corresponding O-sulpho- and O-phospho-derivatives. The acidic amino acid residues may be substituted with any synthetic acidic amino acid, e.g., tetrazolyl derivatives of Gly and Ala. The aliphatic amino acids may be substituted by synthetic derivatives bearing non-natural aliphatic branched or linear side chains C_nH_{2n+2} up to and
25 including n=8. The Met residues may be substituted by norleucine (Nle). The Cys residues may be in D or L configuration and may optionally be substituted with homocysteine (D or L).

[0015] Examples of synthetic aromatic amino acid include, but are not limited to, nitro-Phe, 4-substituted-Phe wherein the substituent is C_1 - C_3 alkyl, carboxyl, hydroxymethyl, sulphomethyl, halo, phenyl, -CHO, -CN, -SO₃H and -NHAc. Examples of synthetic hydroxy containing amino acid, include, but are not limited to, such as 4-hydroxymethyl-Phe, 4-hydroxyphenyl-Gly, 2,6-dimethyl-Tyr and 5-amino-Tyr. Examples of synthetic basic amino acids include, but are not limited to, N-1-(2-pyrazolinyl)-Arg, 2-(4-piperinyl)-Gly, 2-(4-

5 piperinyl)-Ala, 2-[3-(2S)pyrrolinyl]-Gly and 2-[3-(2S)pyrrolinyl)-Ala. These and other synthetic basic amino acids, synthetic hydroxy containing amino acids or synthetic aromatic amino acids are described in Building Block Index, Version 3.0 (1999 Catalog, pages 4-47 for hydroxy containing amino acids and aromatic amino acids and pages 66-87 for basic amino acids; see also <http://www.amino-acids.com>), incorporated herein by reference, by and available from RSP Amino Acid Analogues, Inc., Worcester, MA. Examples of synthetic acid amino acids include those derivatives bearing acidic functionality, including carboxyl, phosphate, sulfonate and synthetic tetrazoyl derivatives such as described by Ornstein et al. (1993) and in U.S. Patent No. 5,331,001, each incorporated herein by reference.

10 [0016] Optionally, in the μ -conopeptides of the present invention, the Asn residues may be modified to contain an N-glycan and the Ser, Thr and Hyp residues may be modified to contain an O-glycan (e.g., g-N, g-S, g-T and g-Hyp). In accordance with the present invention, a glycan shall mean any N-, S- or O-linked mono-, di-, tri-, poly- or oligosaccharide that can be attached to any hydroxy, amino or thiol group of natural or modified amino acids by synthetic or enzymatic methodologies known in the art. The monosaccharides making up the glycan can include D-allose, D-altrose, D-glucose, D-mannose, D-gulose, D-idose, D-galactose, D-talose, D-galactosamine, D-glucosamine, D-N-acetyl-glucosamine (GlcNAc), D-N-acetyl-galactosamine (GalNAc), D-fucose or D-arabinose. These saccharides may be structurally modified, e.g., with one or more O-sulfate, O-phosphate, O-acetyl or acidic groups, such as sialic acid, including combinations thereof. The glycan may also include similar polyhydroxy groups, such as D-penicillamine 2,5 and halogenated derivatives thereof or polypropylene glycol derivatives. The glycosidic linkage is beta and 1-4 or 1-3, preferably 1-3. The linkage between the glycan and the amino acid may be alpha or beta, preferably alpha and is 1-.

15 [0017] Core O-glycans have been described by Van de Steen et al. (1998), incorporated herein by reference. Mucin type O-linked oligosaccharides are attached to Ser or Thr (or other hydroxylated residues of the present peptides) by a GalNAc residue. The monosaccharide building blocks and the linkage attached to this first GalNAc residue define the "core glycans," of which eight have been identified. The type of glycosidic linkage (orientation and connectivities) are defined for each core glycan. Suitable glycans and glycan analogs are described further in U.S. Serial No. 09/420,797 filed 19 October 1999 and in PCT Application No. PCT/US99/24380 filed 19 October 1999 (PCT Published Application No. WO 00/23092), each incorporated herein by reference. A preferred glycan is Gal(β 1 \rightarrow 3)GalNAc(α 1 \rightarrow).

[0018] Optionally, in the μ -conopeptides described above, pairs of Cys residues may be replaced pairwise with isoteric lactam or ester-thioether replacements, such as Ser/(Glu or Asp), Lys/(Glu or Asp), Cys/(Glu or Asp) or Cys/Ala combinations. Sequential coupling by known methods (Barnay et al., 2000; Hruby et al., 1994; Bitan et al., 1997) allows replacement of native Cys bridges with lactam bridges. Thioether analogs may be readily synthesized using halo-Ala residues commercially available from RSP Amino Acid Analogues.

[0019] The present invention is further directed to derivatives of the above peptides and peptide derivatives which are acyclic permutations in which the cyclic permutants retain the native bridging pattern of native toxin. See, for example, Craik et al. (2001).

[0020] The present invention is further directed to a method of treating disorders associated with voltage gated ion channel disorders in a subject comprising administering to the subject an effective amount of the pharmaceutical composition comprising a therapeutically effective amount of a μ -conopeptide described herein or a pharmaceutically acceptable salt or solvate thereof. The present invention is also directed to a pharmaceutical composition comprising a therapeutically effective amount of a μ -conopeptide described herein or a pharmaceutically acceptable salt or solvate thereof and a pharmaceutically acceptable carrier.

[0021] More specifically, the present invention is further directed to uses of these peptides or nucleic acids as described herein as neuromuscular blocking agents, local anesthetic agents, analgesic agents and neuroprotective agents. The μ -conopeptides are also useful for treating neuromuscular disorders.

[0022] The present invention is directed to the use of μ -conopeptides as a local anesthetic for treating pain. The μ -conopeptides have long lasting anesthetic activity and are particularly useful for spinal anesthesia, either administered acutely for post-operative pain or via an intrathecal pump for severe chronic pain situations. The μ -conopeptides are also useful as analgesics in chronic and neuropathic pain states, such as trigeminal neuralgia, diabetic neuropathy, post-herpetic neuralgia, neuroma pain and phantom limb pain. The μ -conopeptides are also useful for treating burn pain and as ocular anesthetics.

[0023] The present invention is directed to the use of μ -conopeptides as neuroprotectants. The μ -conopeptides are useful for the treatment and alleviation of epilepsy and as a general anticonvulsant agent. The μ -conopeptides are also useful for treating neurodegenerative diseases, such as Amyotrophic Lateral Sclerosis (ALS). The μ -conopeptides are further useful as cerebroprotectants, such as for reducing neurotoxic injury associated with

conditions of hypoxia, anoxia or ischemia which typically follows stroke, cerebrovascular accident, brain or spinal cord trauma, myocardial infarct, physical trauma, drowning, suffocation, perinatal asphyxia, or hypoglycemic events.

[0024] The present invention is directed to the use of μ -conopeptides as neuromuscular blockers and for treating neuromuscular disorders. As such, the μ -conopeptides are useful for providing relaxation of muscle, for treating benign essential blepharospasm and other forms of focal dystonia and for anti-wrinkle use.

[0025] More specifically, the present invention is also directed to nucleic acids which encode μ -conopeptides of the present invention or which encodes precursor peptides for these μ -conopeptides, as well as the precursor peptide. The nucleic acid sequences encoding the precursor peptides of other μ -conopeptides of the present invention are set forth in Table 1. Table 1 also sets forth the amino acid sequences of these precursor peptides.

[0026] The present invention is further directed to the use of selectively radioiodinated or radiotriitated μ -conopeptides for characterizing pore occlusion sites on different sodium channel subtypes or for use in screening assays.

[0027] The present invention is also directed to the use of μ -conopeptides for screening small molecule libraries to identify small molecules that are selective blocking agents at specific sodium channel subtypes expressed in mammalian systems. In one embodiment, the blocking activity of a small molecule at a particular sodium channel subtype is compared to the blocking activity of a μ -conopeptide at the same sodium channel subtype. In a second embodiment, the ability of a small molecule to displace a μ -conopeptide from a sodium channel subtype is determined. In a third embodiment, the binding affinity of a small molecule for a sodium channel subtype is compared to the binding affinity of a μ -conopeptide for the same sodium channel subtype.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0028] The present invention is to μ -conopeptides, derivatives or pharmaceutically acceptable salts thereof. The present invention is further directed to the use of this peptide, derivatives thereof and pharmaceutically acceptable salts thereof for the treatment of disorders associated with voltage-gated sodium channels. Thus, the μ -conopeptides or derivatives are useful as neuromuscular blocking agents, local anesthetic agents, analgesic agents and neuroprotective agents. The μ -conopeptides are also useful for treating neuromuscular

disorders. The invention is further directed to nucleic acid sequences encoding the μ -conopeptides and encoding propeptides, as well as the propeptides.

[0029] The present invention, in another aspect, relates to a pharmaceutical composition comprising an effective amount of an μ -conopeptides, a mutein thereof, an analog thereof, an active fragment thereof or pharmaceutically acceptable salts or solvates. Such a pharmaceutical composition has the capability of acting at voltage gated ion channels, and are thus useful for treating a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to the partial or complete blockade of voltage gated ion channels of the central nervous system comprising the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a pharmaceutical composition of the present invention.

[0030] The present invention is directed to the use of μ -conopeptides as neuromuscular blockers and for treating neuromuscular disorders. As such, the μ -conopeptides are useful for providing relaxation of muscle, for treating benign essential blepharospasm and other forms of focal dystonia and for anti-wrinkle use. Thus, in one aspect, the μ -conopeptides are useful as neuromuscular blocking agents in conjunction with surgery or for intubation of the trachea by conventional parenteral administration e.g., intramuscular or intravenous administration in solution. In a second aspect, the μ -conopeptides are useful as agents for treating neuromuscular disorders such as myofacial pain syndrome, chronic muscle spasm, dystonias and spasticity.

[0031] The primary factor detrimental to neurons in neurological disorders associated with deficient oxygen supply or mitochondrial dysfunction is insufficient ATP production relative to their requirement. As a large part of the energy consumed by brain cells is used for maintenance of the Na^+ gradient across the cellular membrane, reduction of energy demand by down-modulation of voltage-gated Na^+ -channels is one strategy for neuroprotection. In addition, preservation of the inward Na^+ gradient may be beneficial because it is an essential driving force for vital ion exchanges and transport mechanisms such as Ca^{2+} homeostasis and neurotransmitter uptake. Thus, the μ -conopeptides of the present invention are useful as neuroprotectants.

[0032] Thus, the pharmaceutical compositions of the present invention are useful as neuroprotectants, especially cerebroprotectants, neuromuscular blockers, analgesics (both as a local anesthetic and for general analgesia use) or adjuvants to general anesthetics. A "neurological disorder or disease" is a disorder or disease of the nervous system including, but

not limited to, global and focal ischemic and hemorrhagic stroke, head trauma, spinal cord injury, hypoxia-induced nerve cell damage as in cardiac arrest or neonatal distress or epilepsy. In addition, a "neurological disorder or disease" is a disease state and condition in which a neuroprotectant, anticonvulsant, analgesic and/or as an adjunct in general anesthesia may be indicated, useful, recommended or prescribed.

[0033] More specifically, the present invention is directed to the use of these compounds for reducing neurotoxic injury associated with conditions of hypoxia, anoxia or ischemia which typically follows stroke, cerebrovascular accident, brain or spinal cord trauma, myocardial infarct, physical trauma, drowning, suffocation, perinatal asphyxia, or hypoglycemic events.

The present invention is further directed to the use of these compounds for treating pain, including acute and chronic pain, such migraine, nociceptive and neuropathic pain.

[0034] A "neuroprotectant" is a compound capable of preventing the neuronal death associated with a neurological disorder or disease. An "analgesic" is a compound capable of relieving pain by altering perception of nociceptive stimuli without producing anesthesia or loss of consciousness. A "muscle relaxant" is a compound that reduces muscular tension. An "adjunct in general anesthesia" is a compound useful in conjunction with anesthetic agents in producing the loss of ability to perceive pain associated with the loss of consciousness.

[0035] The invention relates as well to methods useful for treatment of neurological disorders and diseases, including, but not limited to, global and focal ischemic and hemorrhagic stroke, head trauma, spinal cord injury, hypoxia-induced nerve cell damage such as in cardiac arrest or neonatal distress, epilepsy or other convulsive disorders without undesirable side effects.

[0036] Thus, in one embodiment, the invention provides a method of reducing/alleviating/ decreasing the perception of pain by a subject or for inducing analgesia in a subject comprising administering to the subject an effective amount of the pharmaceutical composition comprising a therapeutically effective amount of a μ -conopeptide described herein or a pharmaceutically acceptable salt or solvate thereof. The pain may be acute, persistent, inflammatory or neuropathic pain. The μ -conopeptides are useful as an analgesia for chronic and neuropathic pain states, such as trigeminal neuralgia, diabetic neuropathy, post-herpetic neuralgia, neuroma pain, phantom limb pain. These peptides are also useful for treating burn pain and as ocular anesthetics.

[0037] In a second embodiment, the invention provides a method of reducing/alleviating/decreasing the perception of pain by a subject or for inducing analgesia, particularly local analgesia, in a subject comprising administering to the subject an effective amount of the pharmaceutical composition comprising a therapeutically effective amount of a μ -conopeptide described herein or a pharmaceutically acceptable salt or solvate thereof. These peptides are also useful for treating burn pain and as ocular anesthetics.

[0038] In a third embodiment, the invention provides a method of treating stroke, head or spinal cord trauma or injury, anoxia, hypoxia-induced nerve cell damage, ischemia, migraine, psychosis, anxiety, schizophrenia, inflammation, movement disorder, epilepsy, any other convulsive disorder or in the prevention of the degenerative changes connected with the same in a subject comprising administering to the subject an effective amount of the pharmaceutical composition comprising a therapeutically effective amount of a μ -conopeptide described herein or a pharmaceutically acceptable salt or solvate thereof.

[0039] In a fourth embodiment, the invention provides a method for providing a neuromuscular block or for treating neuromuscular disorders, such as methods for providing relaxation of muscle, for treating benign essential blepharospasm and other forms of focal dystonia and for anti-wrinkle use. Thus, in one aspect, the μ -conopeptides are useful as neuromuscular blocking agents in conjunction with surgery or for intubation of the trachea by conventional parenteral administration e.g., intramuscular or intravenous administration in solution. In a second aspect, the μ -conopeptides are useful as agents for treating neuromuscular disorders such as myofacial pain syndrome, chronic muscle spasm, dystonias and spasticity.

[0040] The present invention is also directed to the use of μ -conopeptides for screening small molecule libraries to identify small molecules that are selective blocking agents at specific sodium channel subtypes expressed in mammalian systems. In one embodiment, the blocking activity of a small molecule at a particular sodium channel subtype is compared to the blocking activity of a μ -conopeptide at the same sodium channel subtype. In a second embodiment, the ability of a small molecule to displace a μ -conopeptide from a sodium channel subtype is determined. In a third embodiment, the binding affinity of a small molecule for a sodium channel subtype is compared to the binding affinity of a μ -conopeptide for the same sodium channel subtype.

[0041] The μ -conopeptides described herein are sufficiently small to be chemically synthesized. General chemical syntheses for preparing the foregoing ω -conotoxin peptides are

described hereinafter. Various ones of the μ -conopeptides can also be obtained by isolation and purification from specific *Conus* species using the technique described in U.S. Patent Nos. 4,447,356 (Olivera et al., 1984); 5,514,774; 5,719,264; and 5,591,821, as well as in PCT published application WO 98/03189, the disclosures of which are incorporated herein by reference.

[0042] Although the μ -conopeptides of the present invention can be obtained by purification from cone snails, because the amounts of μ -conopeptides obtainable from individual snails are very small, the desired substantially pure μ -conopeptides are best practically obtained in commercially valuable amounts by chemical synthesis using solid-phase strategy. For example, the yield from a single cone snail may be about 10 micrograms or less of μ -conopeptides peptide. By "substantially pure" is meant that the peptide is present in the substantial absence of other biological molecules of the same type; it is preferably present in an amount of at least about 85% purity and preferably at least about 95% purity. Chemical synthesis of biologically active μ -conopeptides peptides depends of course upon correct determination of the amino acid sequence.

[0043] The μ -conopeptides can also be produced by recombinant DNA techniques well known in the art. Such techniques are described by Sambrook et al. (1989). A gene of interest (i.e., a gene that encodes a suitable μ -conopeptides) can be inserted into a cloning site of a suitable expression vector by using standard techniques. These techniques are well known to those skilled in the art. The expression vector containing the gene of interest may then be used to transfect the desired cell line. Standard transfection techniques such as calcium phosphate co-precipitation, DEAE-dextran transfection or electroporation may be utilized. A wide variety of host/expression vector combinations may be used to express a gene encoding a conotoxin peptide of interest. Such combinations are well known to a skilled artisan. The peptides produced in this manner are isolated, reduced if necessary, and oxidized to form the correct disulfide bonds.

[0044] One method of forming disulfide bonds in the μ -conopeptides of the present invention is the air oxidation of the linear peptides for prolonged periods under cold room temperatures or at room temperature. This procedure results in the creation of a substantial amount of the bioactive, disulfide-linked peptides. The oxidized peptides are fractionated using reverse-phase high performance liquid chromatography (HPLC) or the like, to separate peptides having different linked configurations. Thereafter, either by comparing these fractions with the

elution of the native material or by using a simple assay, the particular fraction having the correct linkage for maximum biological potency is easily determined. However, because of the dilution resulting from the presence of other fractions of less biopotency, a somewhat higher dosage may be required.

5 [0045] The peptides are synthesized by a suitable method, such as by exclusively solid-phase techniques, by partial solid-phase techniques, by fragment condensation or by classical solution couplings.

10 [0046] In conventional solution phase peptide synthesis, the peptide chain can be prepared by a series of coupling reactions in which constituent amino acids are added to the growing peptide chain in the desired sequence. Use of various coupling reagents, e.g., dicyclohexylcarbodiimide or diisopropylcarbonyldimidazole, various active esters, e.g., esters of N-hydroxyphthalimide or N-hydroxy-succinimide, and the various cleavage reagents, to carry out reaction in solution, with subsequent isolation and purification of intermediates, is well known classical peptide methodology. Classical solution synthesis is described in detail in the treatise, "Methoden der Organischen Chemie (Houben-Weyl): Synthese von Peptiden," (1974). Techniques of exclusively solid-phase synthesis are set forth in the textbook, "Solid-Phase Peptide Synthesis," (Stewart and Young, 1969), and are exemplified by the disclosure of U.S. Patent 4,105,603 (Vale et al., 1978). The fragment condensation method of synthesis is exemplified in U.S. Patent 3,972,859 (1976). Other available syntheses are exemplified by U.S. 20 Patents No. 3,842,067 (1974) and 3,862,925 (1975). The synthesis of peptides containing γ -carboxyglutamic acid residues is exemplified by Rivier et al. (1987), Nishiuchi et al. (1993) and Zhou et al. (1996).

25 [0047] Common to such chemical syntheses is the protection of the labile side chain groups of the various amino acid moieties with suitable protecting groups which will prevent a chemical reaction from occurring at that site until the group is ultimately removed. Usually also common is the protection of an α -amino group on an amino acid or a fragment while that entity reacts at the carboxyl group, followed by the selective removal of the α -amino protecting group to allow subsequent reaction to take place at that location. Accordingly, it is common that, as a step in such a synthesis, an intermediate compound is produced which includes each of the 30 amino acid residues located in its desired sequence in the peptide chain with appropriate side-chain protecting groups linked to various ones of the residues having labile side chains.

[0048] As far as the selection of a side chain amino protecting group is concerned, generally one is chosen which is not removed during deprotection of the α -amino groups during the synthesis. However, for some amino acids, e.g., His, protection is not generally necessary.

5 In selecting a particular side chain protecting group to be used in the synthesis of the peptides, the following general rules are followed: (a) the protecting group preferably retains its protecting properties and is not split off under coupling conditions, (b) the protecting group should be stable under the reaction conditions selected for removing the α -amino protecting group at each step of the synthesis, and (c) the side chain protecting group must be removable, upon the completion of the synthesis containing the desired amino acid sequence, under reaction conditions that will not undesirably alter the peptide chain.

10 [0049] It should be possible to prepare many, or even all, of these peptides using recombinant DNA technology. However, when peptides are not so prepared, they are preferably prepared using the Merrifield solid-phase synthesis, although other equivalent chemical syntheses known in the art can also be used as previously mentioned. Solid-phase synthesis is commenced from the C-terminus of the peptide by coupling a protected α -amino acid to a suitable resin. Such a starting material can be prepared by attaching an α -amino-protected amino acid by an ester linkage to a chloromethylated resin or a hydroxymethyl resin, or by an amide bond to a benzhydrylamine (BHA) resin or paramethylbenzhydrylamine (MBHA) resin.

15 Preparation of the hydroxymethyl resin is described by Bodansky et al. (1966).

20 Chloromethylated resins are commercially available from Bio Rad Laboratories (Richmond, CA) and from Lab. Systems, Inc. The preparation of such a resin is described by Stewart and Young (1969). BHA and MBHA resin supports are commercially available, and are generally used when the desired polypeptide being synthesized has an unsubstituted amide at the C-terminus. Thus, solid resin supports may be any of those known in the art, such as one having

25 the formulae -O-CH₂-resin support, -N*R*₁ BHA resin support, or -NH-MBHA resin support. When the unsubstituted amide is desired, use of a BHA or MBHA resin is preferred, because cleavage directly gives the amide. In case the N-methyl amide is desired, it can be generated from an N-methyl BHA resin. Should other substituted amides be desired, the teaching of U.S. Patent No. 4,569,967 (Kornreich et al., 1986) can be used, or should still other groups than the

30 free acid be desired at the C-terminus, it may be preferable to synthesize the peptide using classical methods as set forth in the Houben-Weyl text (1974).

[0050] The C-terminal amino acid, protected by Boc or Fmoc and by a side-chain protecting group, if appropriate, can be first coupled to a chloromethylated resin according to the procedure set forth in K. Horiki et al. (1978), using KF in DMF at about 60°C for 24 hours with stirring, when a peptide having free acid at the C-terminus is to be synthesized. Following the coupling of the BOC-protected amino acid to the resin support, the α -amino protecting group is removed, as by using trifluoroacetic acid (TFA) in methylene chloride or TFA alone. The deprotection is carried out at a temperature between about 0°C and room temperature. Other standard cleaving reagents, such as HCl in dioxane, and conditions for removal of specific α -amino protecting groups may be used as described in Schroder & Lubke (1965).

[0051] After removal of the α -amino-protecting group, the remaining α -amino- and side chain-protected amino acids are coupled step-wise in the desired order to obtain the intermediate compound defined hereinbefore, or as an alternative to adding each amino acid separately in the synthesis, some of them may be coupled to one another prior to addition to the solid phase reactor. Selection of an appropriate coupling reagent is within the skill of the art. Particularly suitable as a coupling reagent is N,N'-dicyclohexylcarbodiimide (DCC, DIC, HBTU, HATU, TBTU in the presence of HoBt or HoAt).

[0052] The activating reagents used in the solid phase synthesis of the peptides are well known in the peptide art. Examples of suitable activating reagents are carbodiimides, such as N,N'-diisopropylcarbodiimide and N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide. Other activating reagents and their use in peptide coupling are described by Schroder & Lubke (1965) and Kapoor (1970).

[0053] Each protected amino acid or amino acid sequence is introduced into the solid-phase reactor in about a twofold or more excess, and the coupling may be carried out in a medium of dimethylformamide (DMF):CH₂Cl₂ (1:1) or in DMF or CH₂Cl₂ alone. In cases where intermediate coupling occurs, the coupling procedure is repeated before removal of the α -amino protecting group prior to the coupling of the next amino acid. The success of the coupling reaction at each stage of the synthesis, if performed manually, is preferably monitored by the ninhydrin reaction, as described by Kaiser et al. (1970). Coupling reactions can be performed automatically, as on a Beckman 990 automatic synthesizer, using a program such as that reported in Rivier et al. (1978).

[0054] After the desired amino acid sequence has been completed, the intermediate peptide can be removed from the resin support by treatment with a reagent, such as liquid

hydrogen fluoride or TFA (if using Fmoc chemistry), which not only cleaves the peptide from the resin but also cleaves all remaining side chain protecting groups and also the -amino protecting group at the N-terminus if it was not previously removed to obtain the peptide in the form of the free acid. If Met is present in the sequence, the Boc protecting group is preferably first removed using trifluoroacetic acid (TFA)/ethanedithiol prior to cleaving the peptide from the resin with HF to eliminate potential S-alkylation. When using hydrogen fluoride or TFA for cleaving, one or more scavengers such as anisole, cresol, dimethyl sulfide and methylethyl sulfide are included in the reaction vessel.

[0055] Cyclization of the linear peptide is preferably affected, as opposed to cyclizing the peptide while a part of the peptido-resin, to create bonds between Cys residues. To effect such a disulfide cyclizing linkage, fully protected peptide can be cleaved from a hydroxymethylated resin or a chloromethylated resin support by ammonolysis, as is well known in the art, to yield the fully protected amide intermediate, which is thereafter suitably cyclized and deprotected. Alternatively, deprotection, as well as cleavage of the peptide from the above resins or a benzhydrylamine (BHA) resin or a methylbenzhydrylamine (MBHA), can take place at 0°C with hydrofluoric acid (HF) or TFA, followed by oxidation as described above.

[0056] The peptides are also synthesized using an automatic synthesizer. Amino acids are sequentially coupled to an MBHA Rink resin (typically 100 mg of resin) beginning at the C-terminus using an Advanced Chemtech 357 Automatic Peptide Synthesizer. Couplings are carried out using 1,3-diisopropylcarbodiimide in N-methylpyrrolidinone (NMP) or by 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and diethylisopropylethylamine (DIEA). The FMOC protecting group is removed by treatment with a 20% solution of piperidine in dimethylformamide(DMF). Resins are subsequently washed with DMF (twice), followed by methanol and NMP.

[0057] Muteins, analogs or active fragments, of the foregoing conotoxin peptides are also contemplated here. See, e.g., Hammerland et al. (1992). Derivative muteins, analogs or active fragments of the conotoxin peptides may be synthesized according to known techniques, including conservative amino acid substitutions, such as outlined in U.S. Patent Nos. 5,545,723 (see particularly col. 2, line 50--col. 3, line 8); 5,534,615 (see particularly col. 19, line 45--col. 22, line 33); and 5,364,769 (see particularly col. 4, line 55--col. 7, line 26), each herein incorporated by reference.

[0058] The μ -conopeptides of the present invention are also useful to reduce neurotoxic injury associated with conditions of hypoxia, anoxia or ischemia which typically follows stroke, cerebrovascular accident, brain or spinal chord trauma, myocardial infarct, physical trauma, drownings, suffocation, perinatal asphyxia, or hypoglycemic events. To reduce neurotoxic 5 injury, an ω -conopeptide should be administered in a therapeutically effective amount to the patient within 24 hours of the onset of the hypoxic, anoxic or ischemic condition in order for the μ -conopeptide to effectively minimize the CNS damage which the patient will experience.

[0059] The μ -conopeptides of the present invention are further useful in controlling pain, e.g., as analgesic agents, and the treatment of migraine, acute pain or persistent pain. They can 10 be used prophylactically or to relieve the symptoms associated with a migraine episode, or to treat acute or persistent pain. For these uses, an μ -conopeptide is administered in a therapeutically effective amount to overcome or to ease the pain.

[0060] The μ -conopeptides of the present invention are also useful as neuromuscular blockers and for treating neuromuscular disorders. They can be used for providing relaxation of muscle, for treating benign essential blepharospasm and other forms of focal dystonia and for anti-wrinkle use. Thus, in one aspect, the μ -conopeptides are used as neuromuscular blocking agents in conjunction with surgery or for intubation of the trachea by conventional parenteral administration e.g., intramuscular or intravenous administration in solution. In a second aspect, the μ -conopeptides are used as agents for treating neuromuscular disorders such as myofacial 20 pain syndrome, chronic muscle spasm, dystonias and spasticity. For these uses, a μ -conopeptide is administered in a therapeutically effective amount to relax muscle or provide a neuromuscular block.

[0061] Pharmaceutical compositions containing a compound of the present invention as the active ingredient can be prepared according to conventional pharmaceutical compounding 25 techniques. See, for example, *Remington's Pharmaceutical Sciences*, 18th Ed. (1990, Mack Publishing Co., Easton, PA). Typically, an antagonistic amount of active ingredient will be admixed with a pharmaceutically acceptable carrier. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., intravenous, oral, parenteral or intrathecally. For examples of delivery methods see U.S. Patent No. 5,844,077, incorporated 30 herein by reference.

[0062] "Pharmaceutical composition" means physically discrete coherent portions suitable for medical administration. "Pharmaceutical composition in dosage unit form" means

physically discrete coherent units suitable for medical administration, each containing a daily dose or a multiple (up to four times) or a sub-multiple (down to a fortieth) of a daily dose of the active compound in association with a carrier and/or enclosed within an envelope. Whether the composition contains a daily dose, or for example, a half, a third or a quarter of a daily dose, will 5 depend on whether the pharmaceutical composition is to be administered once or, for example, twice, three times or four times a day, respectively.

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[0063] The term "salt", as used herein, denotes acidic and/or basic salts, formed with inorganic or organic acids and/or bases, preferably basic salts. While pharmaceutically acceptable salts are preferred, particularly when employing the compounds of the invention as medicaments, other salts find utility, for example, in processing these compounds, or where non-medicament-type uses are contemplated. Salts of these compounds may be prepared by art-recognized techniques.

[0064] Examples of such pharmaceutically acceptable salts include, but are not limited to, inorganic and organic addition salts, such as hydrochloride, sulphates, nitrates or phosphates and acetates, trifluoroacetates, propionates, succinates, benzoates, citrates, tartrates, fumarates, maleates, methane-sulfonates, isothionates, theophylline acetates, salicylates, respectively, or the like. Lower alkyl quaternary ammonium salts and the like are suitable, as well.

[0065] As used herein, the term "pharmaceutically acceptable" carrier means a non-toxic, inert solid, semi-solid liquid filler, diluent, encapsulating material, formulation auxiliary of any type, or simply a sterile aqueous medium, such as saline. Some examples of the materials that can serve as pharmaceutically acceptable carriers are sugars, such as lactose, glucose and sucrose, starches such as corn starch and potato starch, cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt, gelatin, talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol, polyols such as glycerin, sorbitol, mannitol and polyethylene glycol; esters such as ethyl oleate and ethyl laurate, agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline, Ringer's solution; ethyl alcohol and phosphate buffer solutions, as well as other non-toxic compatible substances used in pharmaceutical formulations.

[0066] Wetting agents, emulsifiers and lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening,

flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator. Examples of pharmaceutically acceptable antioxidants include, but are not limited to, water soluble antioxidants such as ascorbic acid, cysteine hydrochloride, sodium bisulfite, sodium metabisulfite, sodium sulfite, and the like; oil soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, aloha-tocopherol and the like; and the metal chelating agents such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid and the like.

[0067] For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, lozenges, melts, powders, suspensions or emulsions.

In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, suspending agents, and the like in the case of oral liquid preparations (such as, for example, suspensions, elixirs and solutions); or carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations (such as, for example, powders, capsules and tablets). Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar-coated or enteric-coated by standard techniques. The active agent can be encapsulated to make it stable to passage through the gastrointestinal tract while at the same time allowing for passage across the blood brain barrier. See for example, WO 96/11698.

[0068] For parenteral administration, the compound may be dissolved in a pharmaceutical carrier and administered as either a solution or a suspension. Illustrative of suitable carriers are water, saline, dextrose solutions, fructose solutions, ethanol, or oils of animal, vegetative or synthetic origin. The carrier may also contain other ingredients, for example, preservatives, suspending agents, solubilizing agents, buffers and the like. When the compounds are being administered intrathecally, they may also be dissolved in cerebrospinal fluid.

[0069] A variety of administration routes are available. The particular mode selected will depend of course, upon the particular drug selected, the severity of the disease state being treated and the dosage required for therapeutic efficacy. The methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable,

meaning any mode that produces effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, sublingual, topical, nasal, transdermal or parenteral routes. The term "parenteral" includes subcutaneous, intravenous, epidural, irrigation, intramuscular, release pumps, or infusion.

5 [0070] For example, administration of the active agent according to this invention may be achieved using any suitable delivery means, including:

- (a) pump (see, e.g., Luer & Hatton (1993), Zimm et al. (1984) and Ettinger et al. (1978));
- (b), microencapsulation (see, e.g., U.S. Patent Nos. 4,352,883; 4,353,888; and 5,084,350);
- 10 (c) continuous release polymer implants (see, e.g., U.S. Patent No. 4,883,666);
- (d) macroencapsulation (see, e.g., U.S. Patent Nos. 5,284,761, 5,158,881, 4,976,859 and 4,968,733 and published PCT patent applications WO92/19195, WO 95/05452);
- (e) naked or unencapsulated cell grafts to the CNS (see, e.g., U.S. Patent Nos. 5,082,670 and 5,618,531);
- (f) injection, either subcutaneously, intravenously, intra-arterially, intramuscularly, or to other suitable site; or
- (g) oral administration, in capsule, liquid, tablet, pill, or prolonged release formulation.

[0071] In one embodiment of this invention, an active agent is delivered directly into the CNS, preferably to the brain ventricles, brain parenchyma, the intrathecal space or other suitable 20 CNS location, most preferably intrathecally.

[0072] Alternatively, targeting therapies may be used to deliver the active agent more specifically to certain types of cell, by the use of targeting systems such as antibodies or cell specific ligands. Targeting may be desirable for a variety of reasons, e.g. if the agent is unacceptably toxic, or if it would otherwise require too high a dosage, or if it would not 25 otherwise be able to enter the target cells.

[0073] The active agents, which are peptides, can also be administered in a cell based delivery system in which a DNA sequence encoding an active agent is introduced into cells designed for implantation in the body of the patient, especially in the spinal cord region. Suitable delivery systems are described in U.S. Patent No. 5,550,050 and published PCT 30 Application Nos. WO 92/19195, WO 94/25503, WO 95/01203, WO 95/05452, WO 96/02286, WO 96/02646, WO 96/40871, WO 96/40959 and WO 97/12635. Suitable DNA sequences can

be prepared synthetically for each active agent on the basis of the developed sequences and the known genetic code.

[0074] Exemplary methods for administering such muscle relaxant compounds (e.g., so as to achieve sterile or aseptic conditions) will be apparent to the skilled artisan. Certain methods suitable for administering compounds useful according to the present invention are set forth in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 7th Ed. (1985). The administration to the patient can be intermittent; or at a gradual, continuous, constant or controlled rate. Administration can be to a warm-blooded animal (e.g. a mammal, such as a mouse, rat, cat, rabbit, dog, pig, cow or monkey); but advantageously is administered to a human being. Administration occurs after general anesthesia is administered. The frequency of administration normally is determined by an anesthesiologist, and typically varies from patient to patient.

[0075] The active agent is preferably administered in an therapeutically effective amount. By a "therapeutically effective amount" or simply "effective amount" of an active compound is meant a sufficient amount of the compound to treat the desired condition at a reasonable benefit/risk ratio applicable to any medical treatment. The actual amount administered, and the rate and time-course of administration, will depend on the nature and severity of the condition being treated. Prescription of treatment, e.g. decisions on dosage, timing, etc., is within the responsibility of general practitioners or specialists, and typically takes account of the disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners. Examples of techniques and protocols can be found in *Remington's Pharmaceutical Sciences*.

[0076] Dosage may be adjusted appropriately to achieve desired drug levels, locally or systemically. Typically the active agents of the present invention exhibit their effect at a dosage range from about 0.001 mg/kg to about 250 mg/kg, preferably from about 0.01 mg/kg to about 100 mg/kg of the active ingredient, more preferably from about 0.05 mg/kg to about 75 mg/kg. A suitable dose can be administered in multiple sub-doses per day. Typically, a dose or sub-dose may contain from about 0.1 mg to about 500 mg of the active ingredient per unit dosage form. A more preferred dosage will contain from about 0.5 mg to about 100 mg of active ingredient per unit dosage form. Dosages are generally initiated at lower levels and increased until desired effects are achieved. In the event that the response in a subject is insufficient at such doses, even higher doses (or effective higher doses by a different, more localized delivery

route) may be employed to the extent that patient tolerance permits. Continuous dosing over, for example 24 hours or multiple doses per day are contemplated to achieve appropriate systemic levels of compounds.

[0077] For the treatment of pain, if the route of administration is directly to the CNS, the dosage contemplated is from about 1 ng to about 100 mg per day, preferably from about 100 ng to about 10 mg per day, more preferably from about 1 μ g to about 100 μ g per day. If administered peripherally, the dosage contemplated is somewhat higher, from about 100 ng to about 1000 mg per day, preferably from about 10 μ g to about 100 mg per day, more preferably from about 100 μ g to about 10 mg per day. If the conopeptide is delivered by continuous infusion (e.g., by pump delivery, biodegradable polymer delivery or cell-based delivery), then a lower dosage is contemplated than for bolus delivery.

[0078] Advantageously, the compositions are formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredients. Tablets, coated tablets, capsules, ampoules and suppositories are examples of dosage forms according to the invention.

[0079] It is only necessary that the active ingredient constitute an effective amount, i.e., such that a suitable effective dosage will be consistent with the dosage form employed in single or multiple unit doses. The exact individual dosages, as well as daily dosages, are determined according to standard medical principles under the direction of a physician or veterinarian for use humans or animals.

[0080] The pharmaceutical compositions will generally contain from about 0.0001 to 99 wt. %, preferably about 0.001 to 50 wt. %, more preferably about 0.01 to 10 wt.% of the active ingredient by weight of the total composition. In addition to the active agent, the pharmaceutical compositions and medicaments can also contain other pharmaceutically active compounds. Examples of other pharmaceutically active compounds include, but are not limited to, analgesic agents, cytokines and therapeutic agents in all of the major areas of clinical medicine. When used with other pharmaceutically active compounds, the conopeptides of the present invention may be delivered in the form of drug cocktails. A cocktail is a mixture of any one of the compounds useful with this invention with another drug or agent. In this embodiment, a common administration vehicle (e.g., pill, tablet, implant, pump, injectable solution, etc.) would contain both the instant composition in combination supplementary potentiating agent. The individual drugs of the cocktail are each administered in therapeutically effective amounts. A therapeutically effective amount will be determined by the parameters described above; but, in

any event, is that amount which establishes a level of the drugs in the area of body where the drugs are required for a period of time which is effective in attaining the desired effects.

[0081] The practice of the present invention employs, unless otherwise indicated,
5 conventional techniques of chemistry, molecular biology, microbiology, recombinant DNA,
genetics, immunology, cell biology, cell culture and transgenic biology, which are within the
skill of the art. See, e.g., Maniatis *et al.*, 1982; Sambrook *et al.*, 1989; Ausubel *et al.*, 1992;
Glover, 1985; Anand, 1992; Guthrie and Fink, 1991; Harlow and Lane, 1988; Jakoby and
Pastan, 1979; *Nucleic Acid Hybridization* (B. D. Hames & S. J. Higgins eds. 1984);
10 *Transcription And Translation* (B. D. Hames & S. J. Higgins eds. 1984); *Culture Of Animal*
Cells (R. I. Freshney, Alan R. Liss, Inc., 1987); *Immobilized Cells And Enzymes* (IRL Press,
1986); B. Perbal, *A Practical Guide To Molecular Cloning* (1984); the treatise, *Methods In*
Enzymology (Academic Press, Inc., N.Y.); *Gene Transfer Vectors For Mammalian Cells* (J. H.
Miller and M. P. Calos eds., 1987, Cold Spring Harbor Laboratory); *Methods In Enzymology*,
15 Vols. 154 and 155 (Wu *et al.* eds.), *Immunochemical Methods In Cell And Molecular Biology*
(Mayer and Walker, eds., Academic Press, London, 1987); *Handbook Of Experimental*
Immunology, Volumes I-IV (D. M. Weir and C. C. Blackwell, eds., 1986); Riott, *Essential*
Immunology, 6th Edition, Blackwell Scientific Publications, Oxford, 1988; Hogan *et al.*,
Manipulating the Mouse Embryo, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor,
20 N.Y., 1986).

EXAMPLES

[0082] The present invention is described by reference to the following Examples, which
are offered by way of illustration and are not intended to limit the invention in any manner.
25 Standard techniques well known in the art or the techniques specifically described below were
utilized.

EXAMPLE 1

Isolation of μ -Conopeptides

[0083] Crude venom was extracted from venom ducts (Cruz *et al.*, 1976), and the
components were purified as previously described (Cartier *et al.*, 1996). The crude extract from
venom ducts was purified by reverse phase liquid chromatography (RPLC) using a Vydac C₁₈

semi-preparative column (10 x 250 mm). Further purification of bioactive peaks was done on a Vydac C₁₈ analytical column (4.6 x 220 mm). The effluents were monitored at 220 nm. Peaks were collected, and aliquots were assayed for activity. Throughout purification, HPLC fractions were assayed by means of intracerebral ventricular (i.c.v.) injection into mice (Clark et al., 5 1981).

[0084] The amino acid sequence of the purified peptides were determined by standard methods. The purified peptides were reduced and alkylated prior to sequencing by automated Edman degradation on an Applied Biosystems 477A Protein Sequencer with a 120A Analyzer (DNA/Peptide Facility, University of Utah) (Martinez et al., 1995; Shon et al., 1994).

[0085] In accordance with this method, the μ -conopeptides described as "isolated" in Table 1 were obtained. These μ -conopeptides, as well as the other μ -conopeptides and the μ -conopeptide precursors set forth in Table 1 are synthesized as described in U.S. Patent No. 10 5,670,622.

EXAMPLE 2

Isolation of DNA Encoding μ -Conopeptides

[0086] DNA coding for μ -conopeptides was isolated and cloned in accordance with conventional techniques using general procedures well known in the art, such as described in Olivera et al. (1996). Alternatively, cDNA libraries was prepared from *Conus* venom duct using 20 conventional techniques. DNA from single clones was amplified by conventional techniques using primers which correspond approximately to the M13 universal priming site and the M13 reverse universal priming site. Clones having a size of approximately 300-500 nucleotides were sequenced and screened for similarity in sequence to known μ -conotoxins. The DNA sequences and encoded propeptide sequences are set forth in Table 1. DNA sequences coding for the 25 mature toxin can also be prepared on the basis of the DNA sequences set forth in Table1. An alignment of the μ -conopeptides of the present invention is set forth in Table 2.

TABLE 1

DNA and Amino Acid Sequences of μ -Conopeptides and Precursors

30 **Name:** Ar3.1
 Species: arenatus
 Cloned: Yes

DNA Sequence:

CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTCTTGACCACATCTG
 TATGCTTCTGTTCCCCTTACTGCTCTTCCGCTGGATGGGATCACACCTGCAGACCG
 5 ACCTGCAGAGCGTATGCAGGACGACTTATAACTGAGCATCATCCCCCTGTTGATCC
 TGTCAAACGGTGTGCGAGAGGCCATGCAACATAGGATGCGTACCTGTTGTTAATG
 ACCAGCTTGTATCGCGGCCTCATCAAGCGAATAAGTAAAACGATTGCAGT (SEQ
 ID NO:1)

Translation:

10 MMSKLGVLТИСМЛЛФРЛТАЛПЛДГДQPADRPAЕRMQDDFITEHHPLFDPVKRCCERPC
 NIGCVPCC (SEQ ID NO:2)

Toxin Sequence:

Cys-Cys-Xaa1-Arg-Xaa3-Cys-Asn-Ile-Gly-Cys-Val-Xaa3-Cys-Cys-^ (SEQ ID NO:3)

15
Name: Ak3.1
Species: atlanticus
Cloned: Yes

DNA Sequence:

20 GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCACATGTCTGCTTCTGTTCCAC
 TTACTGCTCTTCCGCTGGATGAAGATCAACCGGTACACCGACCTGCAGAGCGTATGC
 AGGACATTCACTGATCAACATCTCTTGTGATCTCATCAAACGGTGTGCGAGT
 25 TGCCATGCGGGCCAGGCTTGCCTGCTGACATCAATAACGTGTTGATG
 ACCAACTTCTCGAG (SEQ ID NO:4)

Translation:

30 GSMSKLGVLТИСМЛЛФРЛТАЛПЛDEDQPVHRPAЕRMQDISSDQHLFFDLIKRCCELPC
 GPGFCVPCC (SEQ ID NO:5)

Toxin Sequence:

Cys-Cys-Xaa1-Leu-Xaa3-Cys-Gly-Xaa3-Gly-Phe-Cys-Val-Xaa3-Cys-Cys-^ (SEQ ID NO:6)

35
Name: A3.1
Species: aurisiacus
Cloned: Yes

DNA Sequence:

40 CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCACATCTG
 TTTGCTTCTGTTCCCCTTACTGCTCTTCCGATGGATGGAGATCAATCTGAGACCGA
 CCTGAAGAGCGTATGCAGGACGACATTCTGAGCAGCATCCCTGTTAATCAG
 AAAAGAATGTGTTGCGGCGAAGGCCGAAATGCCAGCTATTCAAGAACAGTCA
 45 GATTGTCATTGTTGTTAAATGACAACGTGTCGATGACCAACTCGTTATCAGACT
 AATGAATAAGTAAAACGATTGCAGT (SEQ ID NO:7)

Translation:

MMSKLGVLLTICLLLFPPLTALPMGDQSVDRPEERMQDDISSEQHPLFNQKRMCCGEG
RKCPSYFRNSQICHCC (SEQ ID NO:8)

Toxin Sequence:

Met-Cys-Cys-Gly-Xaa1-Gly-Arg-Lys-Cys-Xaa3-Ser-Xaa5-Phe-Arg-Asn-Ser-Gln-Ile-Cys-His-Cys-Cys-^ (SEQ ID NO:9)

10 **Name:** A3.2

Species: aurisiacus

Cloned: Yes

DNA Sequence:

15 GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTTGCTTCTGTTCCCC
TTACTGCTCTTCCGATCGATGGAGATCAATCTGTAGACCGACCTGCAGAGCGTATGC
AGGATGACATTTCATCTGAGCAGCATCGCTTGTCAATCAGAAAAGAAGGGTGTGC
CGGTGGCCATGCCCGACAATCGACGGTGAATTGTGGCTGTTGCCTGGATGA
TAACCGTGTGATGACCAACTTCTCGAG (SEQ ID NO:10)

Translation:

GSMMMSKLGVLLTICLLLFPPLTALPIDQSVDRPAERMQDDISSEQHRLFNQKRRCCRW
PCPRQIDGEYCGCCLG (SEQ ID NO:11)

Toxin Sequence:

Cys-Cys-Arg-Xaa4-Xaa3-Cys-Xaa3-Arg-Gln-Ile-Asp-Gly-Xaa1-Xaa5-Cys-Gly-Cys-Cys-Leu-# (SEQ ID NO:12)

30 **Name:** A3.3

Species: aurisiacus

Cloned: Yes

DNA Sequence:

35 GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTACTTCTGTTCCCC
TTACTGCTTTCCGATGGATGGAGATCAACCTGCAGACCAACCTGCAGATCGTATGC
AGGACGACATTTCATCTGAGCAGTATCCCTGTTGATAAGAGACAAAAGTGTGCA
CTGGGAAGAAGGGTGTGCTGCTCCGGCAAAGCATGCAAAATCTCAAATGTTGCTCT
GGACGATAACGTGTGATGACCAACTTCTCGAG (SEQ ID NO:13)

Translation:

GSMMMSKLGVLLTICLLLFPPLAFPMGDQPADQPADRMQDDISSEQYPLFDKRQKCCT
GKKGSCSGKACKNLKCCSGR (SEQ ID NO:14)

Toxin Sequence:

Xaa2-Lys-Cys-Cys-Thr-Gly-Lys-Lys-Gly-Ser-Cys-Ser-Gly-Lys-Ala-Cys-Lys-Asn-Leu-Lys-Cys-Cys-Ser-# (SEQ ID NO:15)

5 **Name:** A3.4
Species: aurisiacus
Cloned: Yes

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGCTGACCATCTGTCTGCTTCTGTTCCAC
TTACTGCTGTTCCGCTGGATGGAGATCAACCTCTAGACCGACACGCCGGAGCGTATGC
10 ATGATGGCATTTCACCTAAACGCCATCCCTGGTTGATCCCGTCAAACGGTGTGCA
AGGTGCAATGCGAGTCTTGCACCCCTGTTGCTAACGTGTTGATGACCAACTTCTC
GAG (SEQ ID NO:16)

Translation:

GSMSKLGVLLTICLLFPLTAVPLDGDQPLDRHAERMHDGISPKRHPWFDPVKRCK
VQCESCTPCC (SEQ ID NO:17)

Toxin Sequence:

Cys-Cys-Lys-Val-Gln-Cys-Xaa1-Ser-Cys-Thr-Xaa3-Cys-Cys-^ (SEQ ID NO:18)

15 **Name:** Bn3.1
Species: bandanus
Cloned: Yes

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGCTGACCATCTGTATGCTTCTGTTCCCC
TCACTGCTCTTCCGATGGATGGAGATCAACCTGCAGACCGACCTGCAGAGCGTAGT
CAGGACGTTTCATCTGAACAGCATCCCTGTTGATCCCGTCAAACGGTGTGCAAC
30 TGGCCATGCTCATGGGATGCATCCCTGTTGCTACTATTAAATAACGTGTTGATGAC
CAACTTCTCGAG (SEQ ID NO:19)

Translation:

GSMSKLGVLLTICMLLFPLTALPMGDQPADRPAERSQDVSEHQPLFDPVKRCCNW
35 PCSMGCIPCCYY (SEQ ID NO:20)

Toxin Sequence:

Cys-Cys-Asn-Xaa4-Xaa3-Cys-Ser-Met-Gly-Cys-Ile-Xaa3-Cys-Cys-Xaa5-Xaa5-^ (SEQ ID
NO:21)

40 **Name:** Bt3.1
Species: betulinus
Cloned: Yes

DNA Sequence:

CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCTCTG

TCTGCTTCTGTTCCCTGACTGCTCTCCGCTGGATGAAGATCAACCTGCAGACCG
 ACCTGCAGAGCGTATGCAGGACATTCTCATCTGAACAGCATCCCTGTTGATCCCGT
 CAAACGGTGTGCGAATTGCCATGCCATGGATGCGTCCCTGTTGCTGGCCTTAATA
 ACGTGTGGATGACCAACTGTGTTATCACGCCACGTCAAGTGTCTAATGAATAAGT
 5 AAAATGATTGCAGT (SEQ ID NO:22)

Translation:

MMSKLGVLTFCLLFPLTALPLDEDQPADRPAERMQDISSEQHPLFDPVKRCCELPCH
 GCVPCCWP (SEQ ID NO:23)

Toxin Sequence:

Cys-Cys-Xaa1-Leu-Xaa3-Cys-His-Gly-Cys-Val-Xaa3-Cys-Cys-Xaa4-Xaa3-^ (SEQ ID NO:24)

15 **Name:** Bt3.2
Species: betulinus
Cloned: Yes

DNA Sequence:

20 CAAGAGGGATCGATAGCAGTTCATGATGCTAAACTGGGAGTCTTGTTGACCTCTG
 TCTGCTTCTGTTCCCTGACTGCTCTCCGCTGGATGAAGATCAACCTGCAGACCG
 ACATGCAGAGCGTATGCAGGACATTACCTGAACAGCATCCCTGTTGATCCCGT
 CAAACGGTGTGCGGGCTGCCATGCAATGGATGCGTCCCTGTTGCTGGCCTTCATA
 ACGTGTGGACGACCAACTTGTTATCACGCCACGTCAAGTGTCTGATGAATAAGTA
 AACGATTGCAGT (SEQ ID NO:25)

Translation:

25 MMSKLGVLTFCLLFPLTALPLDEDQPADRHAERMQDISPEQHPSFDPVKRCCGLPCN
 GCVPCCWPS (SEQ ID NO:26)

Toxin Sequence:

30 Cys-Cys-Gly-Leu-Xaa3-Cys-Asn-Gly-Cys-Val-Xaa3-Cys-Cys-Xaa4-Xaa3-Ser-^ (SEQ ID
 NO:27)

35 -----

40 **Name:** Bt3.3
Species: betulinus
Cloned: Yes

DNA Sequence:

45 CAAGAGGGATCGATAGCAGTTCATGATGTTAAACTGGGAGTCTTGTTGACCCTA
 TATGCTTCTGTTCCCTTACTGCTCTCCGCTGGATGGAGATCAACCTGCAGACCAA
 CCTCTAGAGCGCATGCAGTATGACATGTTACGTGCAGTGAATCCCTGGTTGATCCC
 GTCAAAAGGTGCTGCTCGAGGAACTGCGCAGTATGCATCCCTGTTGCCGAATTGG
 CCAGCTTGATTATCGCGGCCAAGAGTCTAATGAATAAGTAAAACGATTGCAGT (SEQ
 ID NO:28)

Translation:

MMFKLGVLLTIYMLLFPTALPLDGDQPADQPLERMQYDMLRAVNPWFDPVKRCCSR
NCAVCIPCCPNWPA (SEQ ID NO:29)

5

Toxin Sequence:

Cys-Cys-Ser-Arg-Asn-Cys-Ala-Val-Cys-Ile-Xaa3-Cys-Cys-Xaa3-Asn-Xaa4-Xaa3-Ala-⁵ (SEQ ID NO:30)

10

Name: Bu3.1
Species: bullatus
Cloned: Yes

15

DNA Sequence:

CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCACATCTG
TCTGCTTCTGTTCCCCTTTGCTCTCCGCAGGATGGAGATCAACCTGCAGACCGA
CCTGCAGAGCGTATGCAGGACGACATTCTGAGCAGAATTCCCTGCTTGAGAA
GAGAGTTACTGACAGGTGCTGCAAAGGGAAGAGGGAATGCCGCAGATGGTGCAGA
GATCACTCGCGTTGTCGCGTCGACGATAAGCTGTTGATGACCAGCTTGTATCAC
GGCTACATCAAGTGTCTAGTGAATAAGTAAAATGATTGCAGT (SEQ ID NO:31)

20

25

Translation:

MMSKLGVLLTICLLLFPFLALPQDGDQPADRPAERMQDDISSEQNSLLEKRVTDRCCKG
KRECGRWCRDHSRCCGRR (SEQ ID NO:32)

30

Name: Bu3.1A
Species: bullatus
Cloned: Yes

35

DNA Sequence:

CAAGAAGGATCGATAGCAGTTCA¹GATGTCTAAACTGGGAGTCTTGTGACCACATCTG
TCTGCTTCTGTTCCCCTTTGCTCTCCGCAGGATGGAGATCAACCTGCAGACCGA
CCTGCAGAGCGTATGCAGGATGACATTCTGAGCAGAATTCCCTGCTTGAGAA
GAGAGTTGGTGACAGGTGCTGCAAAGGGAAGAGGGGGTGCAGATGGTGCAGA
GATCACTCACGTTGTCGCGTCGACGATAACGTGTTGATGACCAGCTTGTATCAC
GGCTACATCAAGTGTCTTAGTGAATAAGTAAAACGATTGCAGT (SEQ ID NO:34)

40

45

Translation:

MMSKLGVLLTICLLLFPFLALRQDGDQPADRPAERMQDDISSEQNPILLEKRGDRCK
GKRGCGRWCRDHSRCCGRR (SEQ ID NO:35)

Toxin Sequence:

Val-Gly-Asp-Arg-Cys-Cys-Lys-Gly-Lys-Arg-Gly-Cys-Gly-Arg-Xaa4-Cys-Arg-Asp-His-Ser-Arg-Cys-Cys-# (SEQ ID NO:36)

5

Name: Bu3.2
Species: bullatus
Cloned: Yes

DNA Sequence:

CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCACATCTG
 TCTGCTTCTGTTCCCCTTTGCTCTTCCGCAGGATGGAGATCAACCTGCAGACCGA
 CCTGCAGAGCGTATGCAGGACGACATTTCATCTGAGCAGAACCTGCTTGAGAA
 GAGAGTTGGTCAAAGGTGCTGCAAAAACGGGAAGAGGGGGTGCAGCAGATGGTGC
 AGAGATCACTCACGTTGTCGGTCGACGATAACGTGTTGATGACCGAGGCTTCGT
 TATCACGGCTACATCAAGTGTCTAGTGAATAAGTAAAACGATTGCAGT (SEQ ID
 NO:37)

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Translation:

MMSKLGVLLTICLLLFPFLALPQDGDQPADRPAERMQDDISSEQNPLLEKRVGERCKN
 GKRGCGRWCRDHSRCCGRR (SEQ ID NO:38)

Toxin Sequence:

Val-Gly-Xaa1-Arg-Cys-Cys-Lys-Asn-Gly-Lys-Arg-Gly-Cys-Gly-Arg-Xaa4-Cys-Arg-Asp-His-Ser-Arg-Cys-Cys-# (SEQ ID NO:39)

30

Name: Bu3.3
Species: bullatus
Cloned: Yes

DNA Sequence:

CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCACATCTG
 TCTGCTTCTGTTCCCCTTTGCTCTTCCGCAGGACGGAGATCAACCTGCAGACCG
 ACCTGCAGAGCGTATGCAGGACGACCTTCATCTGAGCAGCATCCCTGTTGAGAA
 GAGAATTGTTGACAGGTGCTGCAACAAAGGGAACGGGAAGAGGGGGTGCAGCAGA
 TGGTGCAGAGATCACTCACGTTGTCGGTCGACGATGAACGTGTTGATGACCGAGG
 CTTGGTTATCACGGCTACATCAAGTGTCTAGTGAATAAGTAAAACGATTGCAGT
 (SEQ ID NO:40)

40

Translation:

MMSKLGVLLTICLLLFPFLALPQDGDQPADRPAERMQDDLSSEQHPLFEKRVDRCCNK
 GNGKRGCSRWRDHSRCCGRR (SEQ ID NO:41)

45

Toxin Sequence:

Ile-Val-Asp-Arg-Cys-Cys-Asn-Lys-Gly-Asn-Gly-Lys-Arg-Gly-Cys-Ser-Arg-Xaa4-Cys-Arg-Asp-His-Ser-Arg-Cys-Cys-# (SEQ ID NO:42)

5 **Name:** Bu3.4
Species: bullatus
Cloned: Yes

DNA Sequence:

CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCATCTG
TCTGCTTCTGTTCCCTTTGCTCTCCGCAGGATGGAGATCAACCTGCAGACCGA
10 CCTGCTGAGCGTATGCAGGACGACATTCTGAGCGGAATCCCTGTTGAGAAG
AGCGTTGGTTATATTGCTGCCAACCCAAACGGGCAGATGATGTGCGACAG
ATGGTGCAGAAAAAAACTCACGTTGTTGCGGTGACGATAATGTGTTGATGACCAGC
TTTGTATCAAGGCTACATCAAGTATCTAGTGAATAAGTAAAACGATTGCAGT (SEQ
ID NO:43)

15 **Translation:**

MMSKLGVLLTICLLLFPFLALPQDGDQPADRPAERMQDDISERNPLFEKSVGLYCCRP
KPNQMMCDRWCEKNSRCCGRR (SEQ ID NO:44)

20 **Toxin Sequence:**

Val-Gly-Leu-Xaa5-Cys-Cys-Arg-Xaa3-Lys-Xaa3-Asn-Gly-Gln-Met-Met-Cys-Asp-Arg-Xaa4-
Cys-Xaa1-Lys-Asn-Ser-Arg-Cys-Cys-# (SEQ ID NO:45)

25 **Name:** Bu3.5
Species: bullatus
Cloned: Yes

30 **DNA Sequence:**

CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTTTGTGACCATCTG
TCTGCTTCTGTTCCCTTACTGCTCTCCGATGGATGGAGATCAATCTGTAGACCGA
CCTGCAGAACGTATGCAGGACGACCTTCATCTGAGCAGCATCCCTGTTTCAG
AAAAGAAGGTGTTGCGGCGAAGGCTTGACATGCCAGATATTGGAAAAACAGTCA
35 GATTGTGCTTGTAAATGACAACGTGTCGATGACCAACTCGGTATCACGACT
ACGCCAAGTGTCTAATGAATAAGTAAAACGATTGCAGT (SEQ ID NO:46)

40 **Translation:**

MMSKLGVLLTICLLLFPALTALPMGDQSVDRPAERMQDDLSSEQHPLFVQKRRCCGEG
LTCPRYWKNQICACC (SEQ ID NO:47)

45 **Toxin Sequence:**

Arg-Cys-Cys-Gly-Xaa1-Gly-Leu-Thr-Cys-Xaa3-Arg-Xaa5-Xaa4-Lys-Asn-Ser-Gln-Ile-Cys-Ala-
Cys-Cys-^ (SEQ ID NO:48)

Name: Bu3.5A
Species: bullatus
Cloned: Yes

5 DNA Sequence:

CAAGAGGGATCGATGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCATCTG
 TCTGCTTCTGTTCCCTTTGCTCTCCGCAGGATGGAGATCAACCTGCAGACCGA
 CCTGCTGAGCGTATGCAGGACGACATTCTGACATGCCCTGTTGTCAG
 AAAAGAAGGTGTTGCCGAAGGCTTGACATGCCAGATATTGGAAAAACAGTCA
 10 GATTGTGCTGTTAAATGACAACGTGTGATGACCAACTCGGTATCAGACTA
 CGCCAAGTGTCTAATGAATAAGTAAAACGATTGCAGT (SEQ ID NO:49)

15 Translation:

MMSKLGVLITICLLFPLFALPQDGDQPADRPAERMQDDISSEQDPLFVQKRRCCGEGL
 TCPRYWKNQICACC (SEQ ID NO:50)

Toxin Sequence:

Arg-Cys-Cys-Gly-Xaa1-Gly-Leu-Thr-Cys-Xaa3-Arg-Xaa5-Xaa4-Lys-Asn-Ser-Gln-Ile-Cys-Ala-
 Cys-Cys-^ (SEQ ID NO:51)

Name: Cp3.1
Species: capitaneus
Cloned: Yes

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGGTACCCTGCCTGCTTCTGTTCCC
 CTTGCTGCTTCCACTGGATGGAAATCAACCTGCAGACCACCCTGCAAAGCGTAGC
 CAAGATGACAGTTCAGCTGCCCTGATCAATACTGGATTGATCATTCCATTCTGC
 30 TGCAGGGACTGCGGTGAAGATTGTGTTGGTTGCCGGAACGTGTTGATGACCAA
 CTTCTCGAG (SEQ ID NO:52)

Translation:

GSMSKLGVLVTICLLFPLAAFPLDGNQPADHPAKRTQDDSSAALINTWIDHSHSCCR
 35 DCGEDCVGCCR (SEQ ID NO:53)

Toxin Sequence:

Ser-Cys-Cys-Arg-Asp-Cys-Gly-Xaa1-Asp-Cys-Val-Gly-Cys-Cys-Arg-^ (SEQ ID NO:54)

40 Name: Ca3.1
Species: characteristicus
Cloned: Yes

45 DNA Sequence:

CAAGAGGGATCGATGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCATCTG
 TCTGCTTCTGTTCCCTTACTGCTCTCCAATGGATGGAGATCAACCTGCAGACCA

ACCTGCAGATCGTATGCAGGACGACATTCTGAGCAGTATCCCTGTTGATAT
 GAGAAAAAAGGTGTTGGGCCCCGGCGGTTCATGCCCGTATATTCAGAGACAATT
 TTATTGTTGGGTAAATGACAACGTGTCGATGACCAACTCATTATCACGAC
 TACGCCAAGTGTCTAATGAATAAGTAAAATGATTGCAGT (SEQ ID NO:55)

5

Translation:

MMSKLGVLLTICLLLFPALTALPMGDQPADQPADRMQDDISSEQYPLFDMRKRCGP
 GSCPVYFRDNFICGCC (SEQ ID NO:56)

10

Toxin Sequence:

Cys-Cys-Gly-Xaa3-Gly-Gly-Ser-Cys-Xaa3-Val-Xaa5-Phe-Arg-Asp-Asn-Phe-Ile-Cys-Gly-Cys-
 Cys[^] (SEQ ID NO:57)

15

Name: Ca3.2
Species: characteristicus
Cloned: Yes

DNA Sequence:

CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCATCTG
 TCTGCTTCTGTTCCCCTTACTGCTCTCCGATGGATGGAGATGAACCTGCAAACCG
 ACCTGTCAGCGTATGCAGGACAACATTCTGAGCAGTATCCCTGTTGAGAA
 GAGACGAGATTGTTGCACTCCGCCAAGAAATGCAAAGACCGACAATGCAAACCCC
 AGAGATGTTGCGCTGGACGATAACGTGTTGATGACCAACTTATCACGGCTACGTCA
 AGTGTAGTGAATAAGTAAAATGATTGCAGT (SEQ ID NO:58)

20

Translation:

MMSKLGVLLTICLLLFPALTALPMGDDEPANRPVERMQDNISSEQYPLFEKRRDCCTPPK
 KCKDRQCKPQRCCAGR (SEQ ID NO:59)

25

Toxin Sequence:

Arg-Asp-Cys-Cys-Thr-Xaa3-Xaa3-Lys-Lys-Cys-Lys-Asp-Arg-Gln-Cys-Lys-Xaa3-Gln-Arg-
 Cys-Cys-Ala-# (SEQ ID NO:60)

30

Name: Ca3.3
Species: characteristicus
Cloned: Yes

35

DNA Sequence:

CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCATCTG
 TCTGCTTCTGTTCCCCTTACTGCTCTCCACTGGATGGAGATCAACCTGCAGATCAA
 TCTGCAGAGCGACCTGCAGAGCGTACGCAGGACACATTGAGCAGCATCCGTTATA
 TGATCCGAAAAGAAGGTGTTGCCGTTATCCATGCCCGACAGCTGCCACGGATCTG
 CTGCTATAAGTGATAACATGTTGATGCCAGCTTGTTATCACGGCCACGTCAAGTG
 TCTTAATGAATAAGTAAAACGATTGCAGT (SEQ ID NO:61)

40

45

Translation:

MMSKLGVLLTICLLLPLTALPLDGDQPADQSAERPAERTQDDIQQHPLYDPKRRCCRY
PCPDSCHGSCCYK (SEQ ID NO:62)

Toxin Sequence:

Arg-Cys-Cys-Arg-Xaa5-Xaa3-Cys-Xaa3-Asp-Ser-Cys-His-Gly-Ser-Cys-Cys-Xaa5-Lys-^ (SEQ ID NO:63)

10 **Name:** Ca3.4

Species: characteristicus

Cloned: Yes

DNA Sequence:

CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGCCTGTTGACCATCT
GTCTACTTCTGTTTCCCTTAAGTGCTGTTCCGCTGGATGGAGATCAACATGCAGACC
AACCTGCACAGCGTCTGCAGGACCGCATTCCAAGTGAAGATCATCCCTTATTGATC
CCAACAAACGGTGTGCCCCGCCGGCATGCAACATGGGATGCAAGCCTGTTGT
GGATGACCAGCTTGTATCGCGGTCTTCATGAAGTGTCTTAATGAATAAGTAAAAT
GATTGCAGT (SEQ ID NO:64)

Translation:

MMSKLGALLTICLLLFSLTAVPLDGDQHADQPAQRLQDRIPTEHDPLFDPNKRCCPPVA
CNMGCKPCCG (SEQ ID NO:65)

Toxin Sequence:

Cys-Cys-Xaa3-Xaa3-Val-Ala-Cys-Asn-Met-Gly-Cys-Lys-Xaa3-Cys-Cys-# (SEQ ID NO:66)

30 **Name:** Ca3.5

Species: characteristicus

Cloned: Yes

DNA Sequence:

35 CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGCCTGTTGACCATCT
GTCTACTTCTGTTTCCCTTAAGTGCTGTTCCGCTGGATGGAGATCAACATGCAGACC
AACCTGCAGAGCGTCTGCATGACCGCTTCCAAGTGAAAATCATCCCTTATATGATC
CCGTCAAACGGTGTGCGATGATTGCGACTATTCTGCTGGCCTGCTGTA
TGTTGGATAACCTTGTATCGCGGCCTCATCAAGTGTCTAATGAATAAGTAAAAC
40 GATTGCAGT (SEQ ID NO:67)

Translation:

MMSKLGALLTICLLLFSLTAVPLDGDQHADQPAERLHDRLPTENHPLYDPVKRCCDDSE
CDYSCWPCCMFG (SEQ ID NO:68)

Toxin Sequence:

Cys-Cys-Asp-Asp-Ser-Xaa1-Cys-Asp-Xaa5-Ser-Cys-Xaa4-Xaa3-Cys-Cys-Met-Phe-# (SEQ ID

NO:69)

5 **Name:** Ca3.6
Species: characteristicus
Cloned: Yes

DNA Sequence:

10 GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTGCTTCTGTTCCCC
 TTACTGCTGTTCCGCTGGATGGAGATCAACCTGCAGACCGACCTGCAGAGCGTAAG
 CAGGACGTTCATCTGAACAGCATCCCTTCTTGATCCCGTCAAACGGTGTGCCGC
 CGGTGTTACATGGGATGCATCCCTGTTAACGTGTTGATGACCAACTTCTC
 GAG (SEQ ID NO:70)

15 **Translation:**

GSMSKLGVLLTICLLFPLTAVPLDGDQPADRPAERKQDVSEQHPFFDPVKRCCRRC
 YMGCIPCCF (SEQ ID NO:71)

20 **Toxin Sequence:**

Cys-Cys-Arg-Arg-Cys-Xaa5-Met-Gly-Cys-Ile-Xaa3-Cys-Cys-Phe-^ (SEQ ID NO:72)

25 **Name:** Cr3.1
Species: circumcisus
Cloned: Yes

DNA Sequence:

30 CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGGTATTGTTGACCATCT
 GTCTGCTTCTGTTCCCCTACTGCTCTCCAATGGATGGAGATCAACCTGCAGACC
 AACCTGCAGATCGTATGCAGGACGACATTTCATCTGAGCAGTATCCCTGTTGATA
 AGAGACGAAAGTGTGCGGCAAAGACGGCCATGCCCAAATATTCAAAGACAAT
 TTTATTGTGGTTGTTAAATGACAACGTGTCGATGACCAACTCGTTATCACGAT
 TCGCCAAGTGTCTTAATGAATAAGTAAAATGATTGCAGT (SEQ ID NO:73)

35 **Translation:**

MMSKLGVLLTICLLFPLTALPMGDQPADQPADRMQDDISSEQYPLFDKRRKCCGKD
 GPCPKYFKDNFICGCC (SEQ ID NO:74)

40 **Toxin Sequence:**

Arg-Lys-Cys-Cys-Gly-Lys-Asp-Gly-Xaa3-Cys-Xaa3-Lys-Xaa5-Phe-Lys-Asp-Asn-Phe-Ile-Cys-
 Gly-Cys-Cys-^ (SEQ ID NO:75)

45 **Name:** Da3.1
Species: dalli
Cloned: Yes

DNA Sequence:

CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGCCTTGTGACCATCT
 GTCTACTTCTGTTCCCTAAGTCAGTGTCCGCTGGATGGAGATCAACATGCAGACC
 AACCTGCAGAGCGTCTGCAGGACGCCCTCCAAGTGAAAATCATCCCTTATATGATC
 5 CCGTCAAACGGTGTGCGATGATTGGAATGCGACTATTCTGCTGGCCTGCTGTA
 TTTTATCATAACCTTGTATCGCGGCCTCATCAAGTGTCAAATGAATAAGTAAAAT
 GATTGCAGT (SEQ ID NO:76)

Translation:

10 MMSKLGALLTICLLLFSLTAVPLDGDQHADQPAERLQDRLPTENHPLYDPVKRCCDDSE
 CDYSCWPCCILS (SEQ ID NO:77)

Toxin Sequence:

Cys-Cys-Asp-Asp-Ser-Xaa1-Cys-Asp-Xaa5-Ser-Cys-Xaa4-Xaa3-Cys-Cys-Ile-Leu-Ser-^ (SEQ
 15 ID NO:78)

Name: Da3.2
Species: dalli
Cloned: Yes

DNA Sequence:

CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCATTG
 TCTACTTCTGTTCCCTAAGTCAGTGTCCACTGGATGGAGATCAGCCTGCAGACCG
 20 ACCTGCAGAGCGTATGCAGGACGCCCTCATCTGAACATCATCCATTGGATTG
 CGTCAAAAAGAACACAGTGTGCCCCGCCGGTGGCATGCAACATGGGATGCGAGC
 25 CTTGTTGTGGATGACCAGCTTGTATCGCGGCTCATGAAGTGTCTTAATGAATAAG
 TAAAACGATTGCAGT (SEQ ID NO:79)

Translation:

30 MMSKLGVLLTICLLLPLTAVPLDGDQPADRPAERMQDGISSEHHPFFDSVKKKQQCCP
 PVACNMGCEPCCG (SEQ ID NO:80)

Toxin Sequence:

35 Xaa2-Gln-Cys-Cys-Xaa3-Xaa3-Val-Ala-Cys-Asn-Met-Gly-Cys-Xaa1-Xaa3-Cys-Cys-# (SEQ
 ID NO:81)

Name: Da3.3
Species: dalli
Cloned: Yes

DNA Sequence:

CAAGAAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGATCATATG
 45 TCTATTCTGTTCCCTAAGTCAGTGTCCAGCTCAATGGAGATCAGCCTGCAGACCAA
 TCTGCAGAGCGTATGCAGGACAAAATTCTGAACATCATCCCTTTGATCCC
 GTCAAACGTTGTTGCAACGCGGGGTTTGGCCTCGGGATGCACGCCTGTTGG

TGACCAGTTGTTATCGCGGCCTCATCAAGTGTCTAATGAATAAGTAAAATGATTG
CAGT (SEQ ID NO:82)

Translation:

MMSKLGVLIIICLFLFPLTAVQLNGDQPADQSAERMQDKISSEHHPFFDPVKRCCNAGF
CRFGCTPCCW (SEQ ID NO:83)

Toxin Sequence:

Cys-Cys-Asn-Ala-Gly-Phe-Cys-Arg-Phe-Gly-Cys-Thr-Xaa3-Cys-Cys-Xaa4-^ (SEQ ID NO:84)

10

Name: Di3.1
Species: distans
Cloned: Yes

DNA Sequence:

CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGCTGACCATCTT
TCTGCTTCTGTTCCCTTACTGCTGTCGCTGGATGGAGATCAACCCGAGACGG
ACTTGCAGAGCGCATGCAGGACGACAGTTCAGCTGCACTGATTAGAGACTGGCTTC
TTCAAACCCGACAGTGTGTCATCCATGCCATGCACGCCTGCTGTAGATGAC
CAGCTTGTCATCGCGGCTACGTCAAGTATCTAATGAATAAGTAAGTAAAACGATTG
CAGT (SEQ ID NO:85)

Translation:

MMSKLGVLLTIFLLLFPPLTAVPLGDQPADGLAERMQDDSSAALIRDWLQTRQCCVH
PCPCTPCCR (SEQ ID NO:86)

Toxin Sequence:

Xaa2-Cys-Cys-Val-His-Xaa3-Cys-Xaa3-Cys-Thr-Xaa3-Cys-Cys-Arg-^ (SEQ ID NO:87)

30

Name: E3.1
Species: ermineus
Cloned: Yes

DNA Sequence:

ACCTCAAGAGGGATCGATCGCAGTCATGATGTCTAAACTGGGAGCCTGTTGACC
ATCTGTCTGCTTCTGTTCCATTACTGCTCTCTGATGGATGGAGATCAGCCTGCAG
ACCGACCTGCAGAGCGTACGGAGGATGACATTCTGACTACATTCCCTGTTGCA
40 GTTGGCCATGCCCGATACTCCAACGGTAAACTTGTGTTGTTGCTGCCTGGATG
ATAATGTGTTGATGACCAACTTGTATCACGGCTACGTCAAGTGTCTACTGAATAA
GTAAAATGATTGCAGTA (SEQ ID NO:88)

Translation:

MMSKLGALLTICLLFPITALLMDGDQPADRPAERTEDDISSDYIPCCSWPCPRYSNGKL
VCFCLG (SEQ ID NO:89)

Toxin Sequence:

Cys-Cys-Ser-Xaa4-Xaa3-Cys-Xaa3-Arg-Xaa5-Ser-Asn-Gly-Lys-Leu-Val-Cys-Phe-Cys-Cys-Leu-# (SEQ ID NO:90)

5
Name: Ge3.2
Species: generalis
Cloned: Yes

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTGGTTCTGTTCCCC
 TTACTGCTCTTCACTGGATGGAGAACAAACCTGTAGACCGACATGCCGAGCATATGC
 AGGATGACAATTCACTGGATGCCAACCTGTTGCCTCACCTGATAACGTGTTGATGAC
 CAACTTCTCGAG (SEQ ID NO:91)

Translation:

GSMSKLGVL TICLVLFPLTALPLDGEQPVDRHAEHMQDDNSAAQNPWVIAIRQCCT
 FCNFGCQPCCLT (SEQ ID NO:92)

Toxin Sequence:

Xaa2-Cys-Cys-Thr-Phe-Cys-Asn-Phe-Gly-Cys-Gln-Xaa3-Cys-Cys-Leu-Thr-^ (SEQ ID NO:93)

25
Name: Ge3.3
Species: generalis
Cloned: Yes

DNA Sequence:

30 GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTGGTTCTGTTCCCC
 TTACTGCTCTTCACTGGATGGAGAACAAACCTGTAGACCGACATGCCGAGCATATGC
 AGGATGACAATTCACTGGATGCCAGCCTGTTGCGTCCCCTGATAACGTGTTGATGAC
 CAACTTCTCGAG (SEQ ID NO:94)

Translation:

GSMSKLGVL TICLVLFPLTALPLDGEQPVDRHAEHMQDDNSAAQNPWVIAIRQCCT
 FCNFGCQPCCVP (SEQ ID NO:95)

Toxin Sequence:

40 Xaa2-Cys-Cys-Thr-Phe-Cys-Asn-Phe-Gly-Cys-Gln-Xaa3-Cys-Cys-Val-Xaa3-^ (SEQ ID NO:96)

45
Name: μ -GIIA
Species: geographus
Cloned: Yes

DNA Sequence:

GTCGACTCTAGAGGATCCGACAACAAAGAGTCAACCCCCACTGCCACGTCAAGAGCG
 AAGCGCCACAGCTAACAGACAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGG
 5 AGTCTTGTGACCCTGTCTGCTTCTGTTCCCTTAATGCTCTCCGATGGATGGA
 GATGAACCTGCAAACCGACCTGTGAGCGTATGCAGGACAACATTTCATCTGAGCA
 GTATCCCTGTTGAGAAGAGACGAGATTGTTGCACTCCGCCGAAGAAATGCAAAG
 ACCGACAATGCAAACCCCCAGAGATGTTGCGCTGGACGATAACGTGTTGATGACCAA
 10 CTTTATCACGGCTACGTCAAGTGTAGTGAATAAGTAAAATGATTGCAGTCTGCT
 CAGATTGCTTGTGTTGGTCTAAAGATCAATGACCAAACCGTTGTTGATGCG
 GATTGTCATATATTCTCGATTCCAATCCAACACTAGATGATTAAATCACGATAGAT
 TAATTTCATCAATGCCTGATTTCGTCTGTATCAGTTGTTATATTATT
 TTTCGTCACTGTCTACACAAACGCATGCATGCACGCATGCACACACACACACACAA
 15 ACGCTCGCACAAACATGCGCGCACGCACACACACACACACACACACACACACA
 CACACAAGCAATCACACAATTATTGACATTATTATTATTGATTGATGTATTGTTA
 TTCGTTGCTGTTTAGAATAGTTGAGGCCGTCTTGGATTATTGAACACTGC
 TTTATTGTATACGAGTACTCGTGTCTGAAACACTGCTGAAAATAAAACAAACACT
 GACGTAGC (SEQ ID NO:97)

Translation:

MMSKLGVLLTICLLLPLTALPMGDDEPANRPVERMQDNISSEQYPLFEKRRDCCTPPK
 KCKDRQCKPQRCCAGR (SEQ ID NO:98)

Toxin Sequence:

Arg-Asp-Cys-Cys-Thr-Xaa3-Xaa3-Lys-Lys-Cys-Lys-Asp-Arg-Gln-Cys-Lys-Xaa3-Gln-Arg-
 Cys-Cys-Ala-# (SEQ ID NO:99)

Name: μ -GIIIB
 30 Species: geographus
 Isolated: Yes
 Cloned: Yes

DNA Sequence:

35 GGCCAGACGACAACAAAGAGTCAACCCCCACTGCCACGTCAAGAGCGAAGCGCCAC
 AGCTAACAGACAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGT
 GACCATCTGTCTGCTTCTGTTCCCTTAATGCTCTCCGATGGATGGAGATGAACCT
 GCAAACCGACCTGTGAGCGTATGCAGGACAACATTTCATCTGAGCAGTATCCCTTG
 TTTGAGAAGAGACGAGATTGTTGCACTCCGCCAGGAAATGCAAAGACCGACGATG
 40 CAAACCCATGAAATGTTGCGCTGGACGATAACGTGTTGATGACCAACTTATCACG
 GCTAGCTCAGTGTAGTGAATAAGTAAAATGATTGCAGTCTGCTCAGATTGCTTT
 TGTGTTTGGTCTAACAGATCAATGACCAAACCGTTGTTGATGCGGATTGTCTATATA
 TTTCTCGATTCCAATCCAACACTAGATGATTAAATCACGATAGATTAATTTCATCA
 ATGCCTGATTTCGTCTGTCTATCACGTTGTTATTTATTTCGTCAGTGT
 45 CTACACAAACGCATGCATGCACGCATGCACACACGCACGACGCTCGCACAA
 ACATGCGCGCGACGCACACACACACACACACACACACACGAAGCAATC
 ACACAATTAGTTGACATTATTATTATTGATTGATGTATTGTTATTGCTTGT

TTTTAGAATAGTTGAGGCCGTCTTTGGATTATTGAAC TGCTTATTGTATA CG
 AGTACTTCGTGCTTGAAACACTGCTGAAAATAAAACAAACACTGACGTAGCA AAAA
 AAAAAAA (SEQ ID NO:100)

5 **Translation:**
 MMSKLGVLLTICLLLFPALTALPMGDPEANRPVERMQDNISSEQYPLFEKRRDCCTPPR
 KCKDRRKPMKCCAGR (SEQ ID NO:101)

10 **Toxin Sequence:**
 Arg-Asp-Cys-Cys-Thr-Xaa3-Xaa3-Arg-Lys-Cys-Lys-Asp-Arg-Arg-Cys-Lys-Xaa3-Met-Lys-
 Cys-Cys-Ala-# (SEQ ID NO:102)

15 **Name:** μ-GIIIC
Species: geographus
Isolated: Yes

20 **Toxin Sequence:**
 Arg-Asp-Cys-Cys-Thr-Xaa3-Xaa3-Lys-Lys-Cys-Lys-Asp-Arg-Arg-Cys-Lys-Xaa3-Leu-Lys-
 Cys-Cys-Ala-# (SEQ ID NO:103)

25 **Name:** Gm3.1
Species: gloriamaris
Cloned: Yes

30 **DNA Sequence:**
 CTCACTATAGGAATTGAGCTCGGTACACGGGATCGATAGCAGTTCATGATGTCTAA
 ACTGGGAGCCTTGTGACCATCTGTCTACTTCTGTTCCCTAAC TGCTGTTCCGCTG
 GATGGAGATCAACATGCAGACCAACCTGCAGAGCGTCTGCATGACCGCCTCCAAC
 TGAAAATCATCCCTTATATGATCCC GTCAAACGGTGTGCGATGATT CGGAATGCGA
 CTATTCTTGCTGGCCTTGCTGTATGTTGGATAACCTTGTATCGCGGCCTCGATAA
 GTGTCTAATGAATAAGTAAAACGATTGCAGTAGGC (SEQ ID NO:104)

35 **Translation:**
 MMSKLGALLTICLLLFSLTAVPLGDQHADQPAERLHDRLPTENHPLYDPV KRCCDDSE
 CDYSCWPCCMFG (SEQ ID NO:105)

40 **Toxin Sequence:**
 Cys-Cys-Asp-Asp-Ser-Xaa1-Cys-Asp-Xaa5-Ser-Cys-Xaa4-Xaa3-Cys-Cys-Met-Phe-# (SEQ ID
 NO:106)

45 **Name:** Gm3.2
Species: gloriamaris
Cloned: Yes

DNA Sequence:

5 GTTCATGATGTCTAAACTGGGAGTCTTGTGATCATCTGTCTACTTCTGTTCCCCTT
 ACTGCTGTTCCGCTGGATGGAGATCAACCTGCAGACCGATATGCAGAGCGTATGCA
 GGACGACATTCATCTGAACATCATCCCATGTTGATGCCGTAGAGGGTGTGCCA
 TCTGTTGGCATGCCGCTCGGATGCTCGCCTGTTGGTGTGATCAGCTTGTTATCG
 CGGCCTCATCAAGTGAUTCTAATGCAAA (SEQ ID NO:107)

Translation:

10 MMSKLGVLLIICLLLPLTAVPLDGDQPADRYAERMQDDISSEHHPMFDAVRGCCHLA
 CRFGCSPCCW (SEQ ID NO:108)

Toxin Sequence:

15 Gly-Cys-Cys-His-Leu-Leu-Ala-Cys-Arg-Phe-Gly-Cys-Ser-Xaa3-Cys-Cys-Xaa4-^ (SEQ ID
 NO:109)

Name: Gm3.3
Species: gloriamaris
Cloned: Yes

DNA Sequence:

GAGACGACAAGGAACAGTCACCCCCACAGCCACGCCAACAGAGCAGACAGCCACAGC
 TACGTGAAGAAGGGTGGAGAGAGAGGTTCGTGTGATGTTGAAAATGGGAGTGGTGCTATT
 CATCTTCCTGGTACTGTTCCCCCTGGCAACGCTCCAGCTGGATGCAGATCAACCTGT
 AGAACGATATGCGGAGAACAAACAGCTCCTCAACCCAGATGAAAGGAGGGAAATC
 ATATTGCATGCTCTGGGGACGCGATGCTGTTGGATGTGTGCGACCACCCGAGT
 TGTACTTGCTGCGGCCGGTTAGCGCCGAACATCCATGGCGCTGTGCTGGCGGTTTA
 TCCAACAAACGACAGCGTTGATTGATTCATGTATCATTGCGCCCACGTCTCTGTCTA
 30 AGAATGACGAACATGATTGCACTTGTTCAAGATTGCTGTGTTCTTGACAATAA
 ATGACAAAACCTCCAAAAAA (SEQ ID NO:110)

Translation:

MLKMGVVLFIFLVLFPLATLQLDADQPVERYAENKQLNPDERREILHALGTRCCSWD
 35 VCDHPSCTCCGG (SEQ ID NO:111)

Toxin Sequence:

Cys-Cys-Ser-Xaa4-Asp-Val-Cys-Asp-His-Xaa3-Ser-Cys-Thr-Cys-Cys-Gly-# (SEQ ID NO:112)

40 **Name:** La3.1
Species: laterculatus
Cloned: Yes

DNA Sequence:

45 CGACCTCAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGA
 CCATCTGTCTGCTTCTGTTCCCCTACTGCTCTCCGATGGATGGAGATCAACCTGC

AGACCGACCTGCAGAGCGTATGCAGGACGTTCATCTGAACAGCATCCCTGTATG
 ATCCC GTCAAACGGTGTGCGACTGGCCATGCAGCGGATGCATCCCTGTGCTAAT
 AGTAACAACGTGTTGATAACCAACTTCTACCACGACTACGTCAAGTGTCTAATGA
 ATAAGTAAAATGATTGCAGT (SEQ ID NO:113)

5

Translation:

MMSKLGVLLTICLLLFPALTALPMGDQPADRPAERMQDVSEQHPLYDPVKRCCDWPC
 SGCI PCC (SEQ ID NO:114)

10

Toxin Sequence:

Cys-Cys-Asp-Xaa4-Xaa3-Cys-Ser-Gly-Cys-Ile-Xaa3-Cys-Cys-^ (SEQ ID NO:115)

15

Name: La3.2
Species: laterculatus
Cloned: Yes

DNA Sequence:

CGACCTCAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGA
 CCATCTGTCTGCTCTGTTCCCCTACTGCTCTGGATGGAGATCAACCTGCAGACC
 GACTTGCAGAGCGTATGCAGGACAGTCATCTGAGCAGCATCCCTTGAAAAG
 AGACGAGACTGTTGCACACCTCCGAAGAAATGCAGAGACCGACAATGCAAACCTGC
 AC GTTGTGCGGAGGATAACGTGTTGATGACCAACTTGTATCACGGCTACGTCAA
 GTGTCTAGTGAATAAGTAAAACGATTGCAGT (SEQ ID NO:116)

20

Translation:

MMSKLGVLLTICLLLFPALTALDGDQPADRLAERMQDDISSEQHPFEKRRDCCTPPKKCR
 DRQCKPARCCGG (SEQ ID NO:117)

25

Toxin Sequence:

Arg-Asp-Cys-Cys-Thr-Xaa3-Xaa3-Lys-Lys-Cys-Arg-Asp-Arg-Gln-Cys-Lys-Xaa3-Ala-Arg-
 Cys-Cys-Gly-# (SEQ ID NO:118)

30

Name: La3.3
Species: laterculatus
Cloned: Yes

DNA Sequence:

GGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTGC
 TTCTGTTCCCCTACTGCTCTCCGATGGATGGAGATCAACTTGACGCCGATCTGC
 AGAGCGTATGCAGGACAAACATTCTGAGCAGCATCACCTCTTGAAAAGAGAC
 GACCACCATGTTGCACCTATGACGGGAGTTGCCTAAAAGAACATGCATGCGTAAA
 GCTTGTGCGGATGATAACGTGTTGATGACCAACTTGTATCACGGCTACTCAAGT
 45 GTCTAATGAATAAGTAAAATGATTGCAGTA (SEQ ID NO:119)

35

Translation:

MMSKLGVLLTICLLFPLTALPMGDQLARRSAERMQDNISSEQHHLFEKRRPPCCTYD
GSCLKESCMRKACCG (SEQ ID NO:120)

Toxin Sequence:

5 Arg-Xaa3-Xaa3-Cys-Cys-Thr-Xaa5-Asp-Gly-Ser-Cys-Leu-Lys-Xaa1-Ser-Cys-Met-Arg-Lys-
Ala-Cys-Cys-# (SEQ ID NO:121)

10 **Name:** La3.3A

Species: laterculatus

Cloned: Yes

DNA Sequence:

15 GGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCACCTGTCTGC
TTCTGTTCCCTTACTGCTCTCCGATGGATGGAGATCAACTGCACGCCGACCTG
CAGAGCGTATGCAGGACAACATTTCATCTGAGCAGCATTGAAAGGAGA
CGACCACCATGTTGCACCTATGACGGGAGTTGCCTAAAAGAATCATGCAAGCGTAA
AGCTTGTGCGGATAATAACGTGTTGATGACCAACTTGTATCACGGCTACTCAAG
TGTCTAATGAATAAGTAAAATGATTGCAGTA (SEQ ID NO:122)

Translation:

20 MMSKLGVLTTCLLFPLTALPMGDQLARRPAERMQDNISSEQHPFFERRPPCCTYD
GSCLKESCKRKACCG (SEQ ID NO:123)

Toxin Sequence:

25 Arg-Xaa3-Xaa3-Cys-Cys-Thr-Xaa5-Asp-Gly-Ser-Cys-Leu-Lys-Xaa1-Ser-Cys-Lys-Arg-Lys-
Ala-Cys-Cys-# (SEQ ID NO:124)

30 **Name:** Lp3.1

Species: leopardus

Cloned: Yes

DNA Sequence:

35 GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCCTGTCTGCTTCTGTTCCCC
TTACTGCTCTCGGCTGGTGGAGATCAACCTGCAGAGCGACCTGCAAAGCGTACGC
AGGACGACATTCCAGATGGACAGCATCCGTTAAATGATAGGCAGATAAACTGTTGC
CCGTGGCCATGCCCTAGTACATGCCCATCAATGCTGCCATTAAATGATAACGTGTT
GATGACCAACTTCTCGAG (SEQ ID NO:125)

Translation:

40 GSMSKLGVLTVCLLFPLTALRLVGDQPAERPAKRTQDDIPDGQHPLNDRQINCCP
WPCPSTCRHQCCCH (SEQ ID NO:126)

Toxin Sequence:

45 Xaa2-Ile-Asn-Cys-Cys-Xaa3-Xaa3-Xaa4-Xaa3-Cys-Xaa3-Ser-Thr-Cys-Arg-His-Gln-Cys-Cys-His-^
(SEQ ID NO:127)

5 **Name:** Lv3.1
Species: lividus
Cloned: Yes

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCGTCTGTCTGCTTCTGTTCCCC
 TTACTGCTCTCGGCTGGTTAGAGATCAACCTGCAGAGCGACCTGCAAAGCGTACGC
 10 AGGACGACATTCCAAATGGACAGGATCCGTTATTGATAGGCAGATAAATTGTTGC
 CCTTGGCCATGCCCTGATTCATGCCACTATCAATGCTGCCACTGATAACGTGTTGAT
 GACCAACTTCTCGAG (SEQ ID NO:128)

Translation:

15 GSMM SKLG VLL TVCLL FPL TAL RL VRD QPA ERPA KRT QDD I P N G Q DPL IDR Q IN CCPW
 PCP DSCH YQC CH (SEQ ID NO:129)

Toxin Sequence:

20 Xaa2-Ile-Asn-Cys-Cys-Xaa3-Xaa4-Xaa3-Cys-Xaa3-Asp-Ser-Cys-His-Xaa5-Gln-Cys-Cys-His-[~]
 (SEQ ID NO:130)

25 **Name:** L3.1
Species: lynceus
Cloned: Yes

DNA Sequence:

30 AAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTG
 CTTCTGTTCCCCTACTGCTCTCCGATGGATGGAGATCAATCTGCAGACCGACTTG
 CAGAGCGTATGCAGGACAACATT CATCTGAGCAGCATCCCTCTTGAAAAGAGA
 GGACGAGACTGTTGCACACCTCCGAGGAAATGCAGAGACCGAGCCTGCAAACCTCA
 ACGTTGTTGCGGAGGATAAGCTGTTGATGACCAACTTGTATACGGC (SEQ ID
 NO:131)

35 **Translation:**

MMSK LGVLL TICLLL FPL TAL PMD GDQS ADR LAER M QDN IS SEQ HP FFE KR GR DC CT PP
 RK CR DRACK P QRCC G (SEQ ID NO:132)

Toxin Sequence:

40 Gly-Arg-Asp-Cys-Cys-Thr-Xaa3-Xaa3-Arg-Lys-Cys-Arg-Asp-Arg-Ala-Cys-Lys-Xaa3-Gln-
 Arg-Cys-Cys-Gly-# (SEQ ID NO:133)

45 **Name:** M3.1
Species: magus
Cloned: Yes

DNA Sequence:

CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCATCTG
 TCTGCTTCTGTTCCCCTACTGCTCTCCGATGGATGGAGATGAACCTGCAAACCG
 ACCTGTCAGCGTATGCAGGACAACATTGATCTGAGCAGTATCCCTGTTGAGAA
 5 GAGACGAGATTGTTGCACTCCGCCAAGAAATGCAAAGACCGACAATGCAAACCCC
 AGAGATGTTGCGCTGGACGATAACGTGTTGATGACCAACTTATCACGGCTACGTCA
 AGTGTTAGTGAATAAGTAAAATGATTGCACTGCTCAGATTGCTTGTGTTT
 GGTCTAAAGATCAATGACCAAACCGTTGTTGATGCGGATTGTCATATATTCTCG
 ATTCCAATCCAACACTAGATGATTAAATCACGATAAGATTAATTCTATCAATGCCT
 10 TGATTTTCGTCTGTCATATCAGTTGTTATTTTTCGTCACTGTCACAC
 AAACGCATGCATGCACGCATGCACGCACACACGCACGCACGCTCGCACAAACATGC
 GCGGCACGCACACACACACACACACACACACACACACGAAGCAATCACAC
 AATTAGTTGACATTATTATTATTGATGTATTGTTATTGCTTGTGTTT
 AGAATAGTTGAGGCCGTCTTGGATTATTGAACTGCTTATTGTATACGAGTA
 15 CTTCGTGGGGAAACACTGCTGAAAATAAACAAACACTGACGTAGCAAAAAAA
 AAAAAA (SEQ ID NO:134)

Translation:

MMSKLGVLLTICLLFPLTALPMGDDEPANRPVERMQDNISSEQYPLFEKRRDCCTPPK
 KCKDRQCKPQRCCAGR (SEQ ID NO:135)

Toxin Sequence:

Arg-Asp-Cys-Cys-Thr-Xaa3-Xaa3-Lys-Lys-Cys-Lys-Asp-Arg-Gln-Cys-Lys-Xaa3-Gln-Arg-
 Cys-Cys-Ala-# (SEQ ID NO:136)

30 **Name:** M3.2
Species: magus
Cloned: Yes

DNA Sequence:

CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCATCTG
 TCTGCTTCTGTTCCCCTACTGCTCTCCGATGGATGGAGATCAACCTGCAAGACCA
 ACCTGCAAGATCGTATGCAGGACGACATTGATCTGAGCAGTATCCCTGTTGATAT
 35 GAGAAAAAGGTGTTGGCCCCGGCGGTTCATGCCCGTATATTGAGAGACAATT
 TTATTGTTGGTTGTTAAATGACAACGTGTCGATGACCAACTTCATTATCACGAC
 TACGCCAAGTGTCTAATGAATAAATAAAATGATTGAGCTCGCTCAGATTGCTTT
 TGTATTGTTGGCTAAAGATCAATGACCAACCGTTGTTGGATTTGATATA
 40 TTTCTCGAGTCCTATCCAACACTAGATGATTAAATCACGATACTGATTGTTT
 CAAAGGCTGGTTTCTGTCACATCAGTTGTTATATTAAATTTCGTCACT
 GATTACACACACGCATGAACGCACAGAGTACTAACACATACACACACACACACA
 CAC
 CCATCTAGTAGCGCCGCGACGACACACAC (SEQ ID NO:137)

Translation:

MMSKLGVLLTICLLFPLTALPMGDQPADQPADRMQDDISSEQYPLFDMRKRCGPG
 GSCPVYFRDNFICGCC (SEQ ID NO:138)

Toxin Sequence:

Cys-Cys-Gly-Xaa₃-Gly-Gly-Ser-Cys-Xaa₃-Val-Xaa₅-Phe-Arg-Asp-Asn-Phe-Ile-Cys-Gly-Cys-Cys-^ (SEQ ID NO:139)

Name: M3.3
Species: magus
Cloned: Yes

DNA Sequence:

Translation:

MMSKLGVLTLICLLFPLTALPRDGDQSVDRPAERMQDDISSELHPLSIRKRMCCGESAP
CPSYFRNSQICHCC (SEQ ID NO:141)

Toxin Sequence:

Met-Cys-Cys-Gly-Xaa₁-Ser-Ala-Xaa₃-Cys-Xaa₃-Ser-Xaa₅-Phe-Arg-Asn-Gln-Ile-Cys-His-Cys-Cys-[^] (SEQ ID NO:142)

Name: M3.4
Species: magus
Cloned: Yes

DNA Sequence:

CAAGAGGGATCGATAGCAGTCATGATGTCTAAACTGGGAGTCTTGTGACCACATCTG
TCTGCTTCTGTTCCCCCTACTGCTCTCCAATGGATGGAGATCAACCTGCAGACCA
ACCTGCAGATCGTATGCAGGACGACATTCTGAGCAGTATCCCTTGTGATAA
GAGACAAAAGTGTGCGGCCCGGCGGTTCATGCCCGTATATTCACAGACAATT
TATTGTGGTTGTGTTAAATGACAACGTGTCGATGACCAACTTCATTATCAGACT
ACGCCAAGTGTCTAATGAATAAATAATGATTGAGTCAGTCTCGCTCAGATTGCTTT
GTATTGCTAAAGATCAATGACCAAACCGTTGTTGGTGCTGGATTTCATATA
TTCTCGATTCTATCCAACACTAGATGATTAAATCACGATAGATCTGATTGTTAT
CAATGCCTTAATTTTGCTCTGTCATCAGTTGTTATAT (SEQ ID NO:143)

Translation:

MMSKLGVLLTICLLLFPALTALPMGDQPADQPADRMQDDISSEQYPLFDKRQKCCGPG
GSCPVYFTDNFICGCC (SEQ ID NO:144)

Toxin Sequence:

Xaa2-Lys-Cys-Cys-Gly-Xaa3-Gly-Gly-Ser-Cys-Xaa3-Val-Xaa5-Phe-Thr-Asp-Asn-Phe-Ile-Cys-Gly-Cys-Cys-^ (SEQ ID NO:145)

10 **Name:** M3.5
Species: magus
Cloned: Yes

DNA Sequence:

15 CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCACATCTG
TCTGCTTCTGTTCCCCTACTGCTCTCCAATGGATGGAGATCAACCTGCAGACCA
ACCTGCAGATCGTATGCAGGACGACATTTCATCTGAGCAGTATCCCTGTTGATAA
GAGACAAAAGTGTGCGGGCCCCGGCGGTTCATGCCCGTATATTCAGAGACAATT
TATTGTGGTTGTTAAATGACAACGTGTCGATGACCATCTCATTATCACGACT
ACGCCAAGTGTCTAACATAAATAAATGATTGAGCTCGCTCAGATTGCTTT
GTATTTGGTCTAAAGATCAATGACCAAACCGTTGTTGGTGGATTTCATATAT
TTCTCGATTCCATCCAACACTAGATGATTAAATCACGATAGATCTGATTTTT (SEQ
ID NO:146)

Translation:

MMSKLGVLLTICLLLFPALTALPMGDQPADQPADRMQDDISSEQYPLFDKRQKCCGPG
GSCPVYFRDNFICGCC (SEQ ID NO:147)

Toxin Sequence:

30 Xaa2-Lys-Cys-Cys-Gly-Xaa3-Gly-Gly-Ser-Cys-Xaa3-Val-Xaa5-Phe-Arg-Asp-Asn-Phe-Ile-Cys-Gly-Cys-Cys-^ (SEQ ID NO:148)

35 **Name:** U001
Species: magus
Isolated: No

Toxin Sequence:

Xaa2-Lys-Cys-Cys-Ser-Gly-Gly-Ser-Cys-Xaa3-Leu-Xaa5-Phe-Arg-Asp-Arg-Leu-Ile-Cys-Xaa3-Cys-Cys-^ (SEQ ID NO:149)

40 **Name:** Comatose/Death
Species: marmoreus
Isolated: Yes

Toxin Sequence:

Ser-Lys-Gln-Cys-Cys-His-Leu-Ala-Ala-Cys-Arg-Phe-Gly-Cys-Thr-Xaa3-Cys-Cys-Asn-^ (SEQ ID NO:150)

5 **Name:** Mr3.1
Species: marmoreus
Cloned: Yes

DNA Sequence:

10 CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCACATCTG
TCTGCTCTGTTCCGTTACTGCTCTCCGATGGATGGTGTCAACCTGCAGACCGA
CTTGTAGAGCGTATGCAGGACAACATTCTCATCTGAGCAGCATTCCCTCTTGAAAAG
AGAAGAGGAGGCTGTTGCACACCTCCGAGGAAATGCAAAGACCAGCCTGCAAAC
CTGCACGTTGCTGCAGGCCAGGATAACGTGTTGATGACCAACTTGTATCACGGCT
ACGTCAAGTGTCTAGTGAATAAGTAAAACGATTGCAG (SEQ ID NO:151)

Translation:

MMSKLGVLLTICLLLFPVTALPMGDQPADRLVERMQDNISSEQHPFFEKRGGCCTPP
RKCKDRACKPARCCGPG (SEQ ID NO:152)

Toxin Sequence:

Arg-Gly-Gly-Cys-Cys-Thr-Xaa3-Xaa3-Arg-Lys-Cys-Lys-Asp-Arg-Ala-Cys-Lys-Xaa3-Ala-Arg-Cys-Cys-Gly-Xaa3-# (SEQ ID NO:153)

25 **Name:** Mr3.2
Species: marmoreus
Cloned: Yes

DNA Sequence:

30 GAGCTCGGTACCCGACCTCAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTG
GGAATCTGTTGACCATCTGTCTACTTCTATTCCCTTACTGCTGTTCCGCTGGATG
GAGATCAACCTGCAGACCGACCTGCAGAGCGTATGCAGGACGACATTCTCATGAA
CATCATCCCTTTTGATCCCGTCAAACGGTGTGCAGGTATCATGCGGCCTGGGA
35 TGCCACCCCTGTTGATGACCAGCTTGTATCGCGCCTCATCAAGTGTCTAAT
GAATAAGTAAAA (SEQ ID NO:154)

Translation:

40 MMSKLGILLTICLLLFPPLAVPLMDQPADRPAERMQDDISSEHHPFFDPVKRCCRLSCG
LGCHPCCG (SEQ ID NO:155)

Toxin Sequence:

Cys-Cys-Arg-Leu-Ser-Cys-Gly-Leu-Gly-Cys-His-Xaa3-Cys-Cys-# (SEQ ID NO:156)

45 **Name:** Mr3.3
Species: marmoreus

Cloned: Yes

DNA Sequence:

GGCCTACACCAAGCTGCATGCCTGCAGGTCGACTCTAGAGGATCCCCGATCGATA
 5 GCAGTTCATGATGTCTAGACTGGGAGTCTTGTGACCCTGTCTACTTCTGTTCCCG
 CTTACTGCTGTTCCGCTGGATGGAGATCAACCTGCGGACCGACCTGCAGAGCGCCTG
 CAGGACGACATTTCATCTGAACATCATCCCCATTTGATTCCGGAGAGAGTGTTGC
 GGTCGTTCGCATGCCGCTTGGATGCGTGCCTGTTGTATGACCAAGCTTGTTAT
 10 CACGGCCTCATCGAGTGTCTAATGAATAAGTAAAACGATTGCAGTAGGCAGGGTACC
 GAGCTCGAATTCC (SEQ ID NO:157)

Translation:

MMSRLGVLLTICLLLFPPLAVPLDGDQPADRPAERLQDDISSEHHPHFDGSRECCGSFAC
 RFGCVPCCV (SEQ ID NO:158)

Toxin Sequence:

Xaa1-Cys-Cys-Gly-Ser-Phe-Ala-Cys-Arg-Phe-Gly-Cys-Val-Xaa3-Cys-Cys-Val-[^] (SEQ ID NO:159)

Name: Mr3.4

Species: marmoreus

Cloned: Yes

DNA Sequence:

CGACCTCAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGA
 CCATCTGTCTACTTCTATTCCCCCTACTGCTGTTCCGCTGGATGGAGACCAACCTGC
 AGACCGACCTGCAGAGCGTATGCAGGACGACATTTCATCTGAACGTCATCCTTTTT
 TGATCGCAGCAAACAGTGTGCCATCTGCCGGCATGCCGCTCGGATGTACGCCTTG
 30 TTGTTGGTGTACAGCTTGTATCGCGTCCTCATCAAGTGTCTAATGAATAAGTAAA
 ATGATTGCAG (SEQ ID NO:160)

Translation:

MMSKLGVLITCLLLFPPLAVPLDGDQPADRPAERMQDDISSERHPFFDRSKQCCHLPA
 35 CRFGCTPCCW (SEQ ID NO:161)

Toxin Sequence:

Ser-Lys-Gln-Cys-Cys-His-Leu-Xaa3-Ala-Cys-Arg-Phe-Gly-Cys-Thr-Xaa3-Cys-Cys-Xaa4-[^]
 (SEQ ID NO:162)

Name: Mr3.5

Species: marmoreus

Cloned: Yes

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCCTGTCTGCTTCTGTTCCCC

TTACTGCTCTCCGCTGGATGGAGATCAACCTGCAGACCAACGTGCAGAGCGTACG
 CAGGCCGAGAAGCATTCCCTGCCTGATCCGAGAATGGGCTGTTGCCGTTCCATGC
 AAAACCAGTTGCACTACTTGTGTCGGGTGATGATAACGTGTTGATGACCAACTT
 TCTCGAG (SEQ ID NO:163)

5

Translation:

GSMSKLGVLLTICLLLPLTALPLDGDQPADQRAERTQAEKHSLPDRMGCCPFPCKT
 SCTTLCCG (SEQ ID NO:164)

10

Toxin Sequence:

Met-Gly-Cys-Cys-Xaa3-Phe-Xaa3-Cys-Lys-Thr-Ser-Cys-Thr-Thr-Leu-Cys-Cys-# (SEQ ID NO:165)

15

Name: U014
Species: marmoreus
Isolated: Yes

Toxin Sequence:

Cys-Cys-His-Xaa4-Asn-Xaa4-Cys-Asp-His-Leu-Cys-Ser-Cys-Cys-Gly-Ser-^ (SEQ ID NO:166)

20

Name: U017
Species: marmoreus
Cloned: Yes

DNA Sequence:

GCCAAGCTTGCATGCCTGCAGGATGACTCTAGAGGATCCCCACCTCAAGAGGGATC
 GATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTACTTCTGTT
 30 TGCCCTTACTGCTGTTCCGCTGGATGGAGATCAACCTGCAGACCGACCTGCAGAACG
 TATGCAGGACGACATTCTGAACGTCATCCCCTGTTGATGCCGTCAGAGATTG
 TTGCCCGTTGCCGGCATGCCCTTGGATGCAACCCTGTTGGATGACCAGCTTT
 GTTATCGGGACCTCATCAAGTGTCTAATGAATAAGTAAAAACGATTGAGTGGGT
 ACCGAGCTCGAATTCC (SEQ ID NO:167)

35

Translation:

MMSKLGVLLTICLLLPLTAVPLDGDQPADRPAERMQDDISSERHPMFDAVRDCCPLP
 ACPFGCNPCCG (SEQ ID NO:168)

40

Toxin Sequence:

Asp-Cys-Cys-Xaa3-Leu-Xaa3-Ala-Cys-Xaa3-Phe-Gly-Cys-Asn-Xaa3-Cys-Cys-# (SEQ ID NO:169)

45

Name: U019
Species: marmoreus
Isolated: Yes

Toxin Sequence:

Cys-Cys-Ala-Xaa3-Ser-Ala-Cys-Arg-Leu-Gly-Cys-Arg-Xaa3-Cys-Cys-Arg-^ (SEQ ID NO:170)

5 **Name:** U020

Species: marmoreus

Isolated: Yes

Toxin Sequence:

Cys-Cys-Ala-Xaa3-Ser-Ala-Cys-Arg-Leu-Gly-Cys-Arg-Xaa3-Cys-Cys-Arg-^ (SEQ ID NO:171)

15 **Name:** U022

Species: marmoreus

Isolated: Yes

Toxin Sequence:

Cys-Cys-Ala-Xaa3-Ser-Ala-Cys-Arg-Leu-Gly-Cys-Arg-Xaa3-Cys-Cys-Arg-^ (SEQ ID NO:172)

20 **Name:** U024

Species: marmoreus

Isolated: Yes

Toxin Sequence:

Gly-Cys-Cys-Gly-Ser-Phe-Ala-Cys-Arg-Phe-Gly-Cys-Val-Xaa3-Cys-Cys-Val-^ (SEQ ID NO:173)

30 **Name:** Nb3.1

Species: nobilis

Cloned: Yes

DNA Sequence:

35 GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTACTTCTGTTCCCC
 TTACTGCTCTTCGCTGGATGAAGATCAACCGGTACACCGACCTGCAGAGCGTATGC
 AGGACATTTCATCTGATCAACATCTCTTGTCTCATCAAACGGTGCTGCGAGT
 TGCCATGCGGGCCAGGCTTTGCGTCCCTTGTGCTGACATCAATAACGTGTTGATG
 40 ACCAACTTCTCGAG (SEQ ID NO:174)

Translation:

45 GSMMMSKLGVLLTICLLLFPALTALPLDEDQPVHRPAERMQDISSDQHLFFDLIKRCCELPC
 GPGFCVPCC (SEQ ID NO:175)

Toxin Sequence:

Cys-Cys-Xaa1-Leu-Xaa3-Cys-Gly-Xaa3-Gly-Phe-Cys-Val-Xaa3-Cys-Cys-^ (SEQ ID NO:176)

5 **Name:** Nb3.2
Species: nobilis
Cloned: Yes

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTACTTCTGTTCCCC
 TTACTGCTTTCCGATGGATGGAGATCAACCTGCAGACCAACCTGCAGATCGTATGC
 10 AGGACGACATTTCATCTGAGCAGTATCCCTGTTGATAAGAGACAAAAGTGTGCA
 CTGGGAAGAAGGGGTATGCTCCGGCAAAGCATGCAAAATCTCAAATGTTGCTCT
 GGACGATAACGTGTTGATGACCAACTTCTCGAG (SEQ ID NO:177)

Translation:

15 GSMM SKLG VLL TIC LLL FPL TAF PMD QP ADQ PAD RM QDD IS SE QY PL FD KR QKC CT
 GKG SCS GKACK NLK CCS GR (SEQ ID NO:178)

Toxin Sequence:

20 Xaa2-Lys-Cys-Cys-Thr-Gly-Lys-Lys-Gly-Ser-Cys-Ser-Gly-Lys-Ala-Cys-Lys-Asn-Leu-Lys-
 Cys-Cys-Ser-# (SEQ ID NO:179)

25 **Name:** Pu3.1
Species: pulicarius
Cloned: Yes

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTTTGTGACCATCTGTCTGCTTCTGTTCCCC
 TTACTGCTGTTCCGCTGGATGGAGATCAACCTGCAGACCGACCTGCAGAGCGTATGC
 30 AGGACATTGCAACTGAACAGCATCCCTTGTGCTTAGTAATAACGTGTTGATGACCAAC
 GCTGTTACATGGGATGCATCCCTTGTGCTTAGTAATAACGTGTTGATGACCAAC
 TTTCTCGAG (SEQ ID NO:180)

Translation:

35 GSMM SKLG VLL TIC LLL FPL AVPL DGD QP ADR PAER M QDI ATE QHP FF DPV KRCC NSC
 YMGCIPCCF (SEQ ID NO:181)

Toxin Sequence:

40 Cys-Cys-Asn-Ser-Cys-Xaa5-Met-Gly-Cys-Ile-Xaa3-Cys-Cys-Phe-^ (SEQ ID NO:182)

45 **Name:** Qc3.1
Species: quercinus
Cloned: Yes

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTGCTTCTGTTCCCC

TTACAGCTCTCAGCTGGATGGAGATCAACCTGCAGACCGACCTGCAGAGCGTACG
 CAGGACATTGCATCTGAACAGTATCGAAAGTTGATCAGAGAACAGAGGTGTTGCCA
 GTGGCCATGCCCGTAGTTGCAGATGCTGCCGTACTGGTTAACGTGTTGATGACCA
 ACTTTCTCGAG (SEQ ID NO:183)

5

Translation:

GSMMSKLGVLLTICLLFPLTALQLDGDQPADRPAERTQDIASEQYRKFDQRQRCCQW
 PCPGSCRCCRTG (SEQ ID NO:184)

10

Toxin Sequence:

Xaa2-Arg-Cys-Cys-Gln-Xaa4-Xaa3-Cys-Xaa3-Gly-Ser-Cys-Arg-Cys-Cys-Arg-Thr-# (SEQ ID NO:185)

15

Name: QcIIIA
Species: quercinus
Isolated: Yes

Toxin Sequence:

Cys-Cys-Ser-Gln-Asp-Cys-Leu-Val-Cys-Ile-Xaa3-Cys-Cys-Xaa3-Asn-# (SEQ ID NO:186)

20

Name: QcIIIB
Species: quercinus
Isolated: Yes

Toxin Sequence:

Cys-Cys-Ser-Arg-His-Cys-Xaa4-Val-Cys-Ile-Xaa3-Cys-Cys-Xaa3-Asn-? (SEQ ID NO:187)

30

Name: R3.1
Species: radiatus
Isolated: Yes
Cloned: Yes

35

DNA Sequence:

TCAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCATCT
 GTCTGCTTCTGTTCCCCTACTGCTCTCGATGGATGGAGATCAACCTGTAGACCG
 ACTTGCAGAGCGTATGCAGGACAACATTTCATCTGAGCAGCATAACCTTCTTGAAAA
 40 GAGACTACCATCGTGTGCTCCCTTAACTTGCGGGCTTGCCCCAGTACCAGCATGCAA
 ACGTAACCCTGTTGCACAGGATAACGTGTTGATGACCAACTTGTATCACGGCTA
 CGTCAAGTGTCTAGTGAATAAGTAAAACATTGCAGT (SEQ ID NO:188)

40

Translation:

MMSKLGVLLTICLLFPLTALPMDGDQPVDRLAERMQDNISSEQHTFFEKRLPSCCSLN
 LRLCPVPACKRNPCCTG (SEQ ID NO:189)

Toxin Sequence:

Leu-Xaa3-Ser-Cys-Cys-Ser-Leu-Asn-Leu-Arg-Leu-Cys-Xaa3-Val-Xaa3-Ala-Cys-Lys-Arg-Asn-Xaa3-Cys-Cys-Thr-# (SEQ ID NO:190)

5

Name: R3.2
Species: radiatus
Cloned: Yes

10 **DNA Sequence:**

AGGTCGACTCTAGAGGATCCCCAAGGATCGATAGCAGTTCATGATGTCTAAACTGG
 GAGTCTTGTGACCATCTGCTGCTTCTGTTCCCTTAATGCTCTCCGATGGATGG
 AGATCAACCTGCAGACCGACTTGCAGAGCGTATGCAGGACGACATTTCATCTGAGC
 AGCATCCCTCTTAAAAAGAGACAACAAAGATGTTGCACCGTTAACAGGAGTTGT
 CCAGTACCAAGCATGCAGAAGTAAACCTTGTGCAAATCATAACGTATTGATGACCA
 ACTTTGTTATCACGGCTACGTCAAGTGTCTAGTGAATAAGTAAAATGATTGCAG
 (SEQ ID NO:191)

15

Translation:

MMSKLGVLLTICLLLFPALTALPMGDQPADRLAERMQDDISSEQHPFFKKRQQRCCTV
 KRICPVPACRSKPCCKS (SEQ ID NO:192)

20

Toxin Sequence:

Xaa2-Gln-Arg-Cys-Cys-Thr-Val-Lys-Arg-Ile-Cys-Xaa3-Val-Xaa3-Ala-Cys-Arg-Ser-Lys-Xaa3-Cys-Cys-Lys-Ser-^ (SEQ ID NO:193)

25

Name: R3.3
Species: radiatus
Cloned: Yes

30

DNA Sequence:

ACCTCAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACC
 ATCTGTCGCTCTGTTCCCGTTACTGCTCTCCGATGGATGGTGATCAACCTGCAG
 35 ACCGACTTGTAGAGCGTATGCAGGACAACATTTCATCTGAGCAGCAGTCCCTCTTG
 AAAAGAGAAGAGAGGAGGCTGTTGCACACCTCCGAGGAAATGCAAAGACCGAGCCTG
 CAAACCTGCACGTGCTGCCAGGATAACGTGTTGATGACCAACTTGTTATCA
 CGGCTACGTCAAGTGTCTAGTGAATAAGTAAAACGATTGCAGT (SEQ ID NO:194)

40

Translation:

MMSKLGVLLTICLLLFPVTALPMGDQPADRLVERMQDNISSEQHPFFEKRQRRGGCCTPP
 RKCKDRACKPARCCPG (SEQ ID NO:195)

35

Toxin Sequence:

Arg-Gly-Gly-Cys-Cys-Thr-Xaa3-Xaa3-Arg-Lys-Cys-Lys-Asp-Arg-Ala-Cys-Lys-Xaa3-Ala-Arg-Cys-Cys-Gly-Xaa3-# (SEQ ID NO:196)

5 **Name:** Ra3.1
Species: *rattus*
Cloned: Yes

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGGTGACCATCTGCCTGCTTCTGTTCCCT
CTTGCTGCTTTCCACTGGATGGAGATCAACCTGCAGACCACCCTGCAAAGCGTACG
10 CAAGATGACAGTTCAGCTGCCCTGATCAATGCCTGGCTTGATGAATCCCAGACTTGC
TGCAGTAACTGCGGTGAAGATTGTGATGGTTGTTGCCAGTAACGTGTTGATGACCAA
CTTCTCGAG (SEQ ID NO:197)

15 **Translation:**

GSMMSKLGVLVTICLLLPLAAFPLDGDQPADHPAKRTQDDSSAALINAWLDESQTCCS
NCGEDCDGCCQ (SEQ ID NO:198)

20 **Toxin Sequence:**

Xaa2-Thr-Cys-Cys-Ser-Asn-Cys-Gly-Xaa1-Asp-Cys-Asp-Gly-Cys-Cys-Gln-^ (SEQ ID
NO:199)

25 **Name:** Sm3.1
Species: *stercusmuscarum*
Cloned: Yes

DNA Sequence:

30 GACCTCAAGAGGGATCGATAGCAGTTCTGATGTCTAAACTGGGAGTCTTGTGAC
CATCTGTCTGCTTCTGTTCTCTTACTGCTCTCCGATGGATGGAGATCAACCTGCA
GACCAACCTGCAGATCGTATGCAGGACGACATTCTGAGCAGTATCCCTTGTGTT
GATAAGAGACAAAAGTGTGCACTGGGAAGAAGGGGTATGCTCCGGCAAAGCAT
GCAAAAATCTCAAATGTTGCTCTGGACGATAACGTGTTGATGACCAACTTGTATC
ACGGCTACGTCAAGTGTCTAATGAATAAGTAAAACGATTGCAGT (SEQ ID NO:200)

35 **Translation:**

MSKLGVLVTICLLLPLTALPMDGDQPADQPADRMQDDISSEQYPLFDKRQKCCTGKK
GCSKGACKNLKCCSGR (SEQ ID NO:201)

40 **Toxin Sequence:**

Xaa2-Lys-Cys-Cys-Thr-Gly-Lys-Lys-Gly-Ser-Cys-Ser-Gly-Lys-Ala-Cys-Lys-Asn-Leu-Lys-
Cys-Cys-Ser-# (SEQ ID NO:202)

45 **Name:** U034
Species: *stercusmuscarum*
Isolated: Yes
Cloned: Yes

DNA Sequence:

GATCGATAGCAGTCGTGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTGCTT
 CTGTTCCCTTAAGTGCCTCCGATGGATGGAGATCAACCTGCAGACCAACCTGCA
 5 GATCGTATGCAGAACGACATTCTGAGCAGTATCCCTGTTGATAAGAGACAA
 AAGTGTGCGGCCGGCGCGTCATGCCAGATATTCAAAGACAATTATTGT
 GGTTGTTGTTAAATGACAACGTGTCGATGACCAACTCGTTACGACTTCGCCAA
 GTGTCTAATGAATAAGTAAAACGATTGCAGT (SEQ ID NO:203)

Translation:

MSKLGVLLTICLLLFPALTALPMGDQPADQPADRMQNDISSEQYPLFDKRQKCCGP GAS
 CPRYFKDNFICGCC (SEQ ID NO:204)

Toxin Sequence:

Xaa2-Lys-Cys-Cys-Gly-Xaa3-Gly-Ala-Ser-Cys-Xaa3-Arg-Xaa5-Phe-Lys-Asp-Asn-Phe-Ile-
 Cys-Gly-Cys-Cys-^ (SEQ ID NO:205)

Name: S3.1

Species: striatus

Cloned: Yes

DNA Sequence:

CGACCTTCAAGAGGGATCGATAGCAGTCGCGATGTCTAAACTGGGGTATTGTTG
 ACCATCTGCTGCTCTGTTCCCTTAAGTGCAGGACATTCTGAGCAGTATCCCTCGT
 CAGACCAACTGAAGATCGTATGCAGGACGACATTCTGAGCAGTATCCCTCGT
 TTGTTAGGAGACAAAGTGTGCGCGAAGGCTCGTCATGCCAAATATTCAA
 AACAAATTATTGTGGTTGTTAAATGACAACGTGTCGATGACCAACTCGTTA
 TCACGACTACGCCAAGTGTCTGCTAATGATAATAAAATGATTCC (SEQ ID NO:206)

Translation:

MSKLGVLLTICLLLFPALTALPMDEDQPADQLEDRMQDDISSEQYPSFVRRQKCCGEGSS
 CPKYFKNNFICGCC (SEQ ID NO:207)

Toxin Sequence:

Xaa2-Lys-Cys-Cys-Gly-Xaa1-Gly-Ser-Ser-Cys-Xaa3-Lys-Xaa5-Phe-Lys-Asn-Asn-Phe-Ile-Cys-
 Gly-Cys-Cys-^ (SEQ ID NO:208)

Name: S3.2

Species: striatus

Cloned: Yes

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCCTGCTGTCTGCTTCTGTTCCCC
 TTACTGCTCTCCGCTGGATGGAGATCAACCTGCAGACCGACCTGCAGAGCGTATGC
 AGGACGACATTCTGACGAGCATCCCTGTTGATAAGAGACAAAATGTTGCA

ATGGGGGATGCTCCAGCAAATGGTGCAGAGATCACGCACGTTGTCGGTCGATGA
TAACGTGTTGATGACCAACTTCTCGAG (SEQ ID NO:209)

Translation:

GSMMSKLGVLTVCLLFPLTALPLGDQPADRPAERMQDDISSDEHPLFDKRQNCCN
GGCSSKWCRDHARCCGR (SEQ ID NO:210)

Toxin Sequence:

Xaa2-Asn-Cys-Cys-Asn-Gly-Gly-Cys-Ser-Ser-Lys-Xaa4-Cys-Arg-Asp-His-Ala-Arg-Cys-Cys-#
(SEQ ID NO:211)

Name: Ts3.1
Species: tessulatus
Cloned: Yes

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATGTGTCTGCTTCTGTTCCCC
TTACTGCTGTTCCGCTGGATGGAGATCAACCTGCAGACCGACCTGCAGAGCGTAGG
CAGGACATTGCAACTGACGATCATCCTTGTTGATCCCGTCAAACGGTGCTGCCAC
AAATGCTATATGGGATGCATCCCTGTTGCATTAGTAACGTGTTGATGACCAACTT
TCTCGAG (SEQ ID NO:212)

Translation:

GSMMSKLGVLTMCLLFPLTAVPLDGDPADRPAREQQDIATDDHPLFDPVKRCCCHK
CYMGCIPCCI (SEQ ID NO:213)

Toxin Sequence:

Cys-Cys-His-Lys-Cys-Xaa5-Met-Gly-Cys-Ile-Xaa3-Cys-Cys-Ile-^ (SEQ ID NO:214)

Name: Ts3.2
Species: tessulatus
Cloned: Yes

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTGTGCTTCTGTTCCCC
TTACTGCTGTTCCGCTGGATGGAGATCAACCTGCAGACCAACCTGCAGAGCGTAGG
CAGAACGAGCAGCATCCCTGTATGATCAGAAAAGAAAGTGTGCCGGCCGCCATG
40 CGCCATGAGCTGCGGCATGGCTAGGTGTTGCTATTAATGATAACGTGTTGATGACCA
ACTTCTCGAG (SEQ ID NO:215)

Translation:

GSMMSKLGVLVICVLLFPLTAVPLDGDPADQPAERTQNEQHPLYDQKRKCCRPPCA
45 MSCGMARCCY (SEQ ID NO:216)

Toxin Sequence:

Lys-Cys-Cys-Arg-Xaa₃-Xaa₃-Cys-Ala-Met-Ser-Cys-Gly-Met-Ala-Arg-Cys-Cys-Xaa₅-^ (SEQ ID NO:217)

5 **Name:** Circling
Species: textile
Isolated: Yes
Cloned: Yes

10 **DNA Sequence:**

GAGTCACCCACTGTCACGCCAAGAGCGGACGCCACAGCTAACGGCAAGAAGGATC
GATAGCAGTTCATGATGTCTAAACTGGGAGCCTGTTGACCATCTGTCTACTTCTGT
TTTCCCTTACTGCTGTTCCGCTGGATGGAGATCAACATGCAGACCAACCTGCACAGC
GTCTGCAGGACCGCATTCCAACCTGAAGATCATCCCTTATTGATCCAACAAACGGT
15 GTTGCCGCCGGTGGCATGCAACATGGGATGCAAGCCTGTTGGATGACCAGCTT
TGTATCGCGGTCTCATGAAGTGTCTAATGAATAAGTAAAACGATTGCAGTTCGTT
CAGATTGCTGTTGTATTTGGTCTAAAGATTAATGACCAAACCTGTTCTTGATCCG
GATTTCACGTATTCTCGATTCCATTCAACACTAGATAAGTTAACGACAGAT
CTGATTTCCATCAATGCCTGCTTTGGTCTGTCATATAAAATCTGTTATATTAA
20 TTCTCGTCACTTCAACACGCACACACACACACACACGCGCGC (SEQ ID NO:218)

25 **Translation:**

MMSKLGALLTICLLLFSLTAVPLGDQHADQPAQRLQDRIPTEDHPLFDPNKRCCPPVA
CNMGCKPCCG (SEQ ID NO:219)

30 **Toxin Sequence:**

Cys-Cys-Xaa₃-Xaa₃-Val-Ala-Cys-Asn-Met-Gly-Cys-Lys-Xaa₃-Cys-Cys-Gly-^ (SEQ ID NO:220)

35 **Name:** Scratcher I
Species: textile
Cloned: Yes

40 **DNA Sequence:**

GGATCCAGACGACAAAGAAGAGTCACCCACTGCCACGTCAAGAGCAGAGCCCCAC
AGCTAACAGACAAGAAGGATCGATAGCAGTTCATGATGTTAAACTGGGAGTCTGTT
GACCATCTGTCTCCTCTGTTCCCTTAATGCTGTTCCGGTGGAGATCAACCT
45 GCAGACCAACCTGCAGAGCGTCTGCTGGACGACATTTCATTGAAAATAATCCCTT
TATGATCCGCCAAACGGTGTGCAGGACTTGCTCGGTTGCACACCTTGTGGA
TGACCAGCCTCATCAAGTGTCTAACGAATAAGI AAAGCGATTGCAGTCTCGTTCA
ATTACTTTGTATTCTGGTCTAAAGATTAATGACCAAACCTCTTCTTGATCCGGAT
GTACATATATTCTCGATTCCATCCAACGCTAGATAAGCTAACGACAGATCTG
45 ATTCTGTCAATGCCTGCTTTGGTCTCTCATATCACTCTGTTATTTAATT
CTCGTCACTATATATATACACACACACACACGGAATTCCGATTGTCCAGTA
CCGTTCTGGATCGAGGTATTGCTGCGATGGCTATTCTGTACTCTTCTGCG

CTTGATAGTGTCTTCACTCCCACAGGCCAGCCAAGAGCAGACAGCCACAGCTACGTGAAGA
 CGTGTGCCCTCACTGGTTATAAAACCCCTGATCCTACTCTCTGGACGCCTCGGGG
 GCCCAACCTCCAAATAAAGCGACATCCAATGAAAAAA (SEQ ID NO:221)

5 **Translation:**

MMFKLGVLTLICLLLFSLNAVPLDGDQPADQPAERLLDDISFENNPFYDPAKRCCRTCF
 GCTPCCG (SEQ ID NO:222)

10 **Toxin Sequence:**

Cys-Cys-Arg-Thr-Cys-Phe-Gly-Cys-Thr-Xaa3-Cys-Cys-# (SEQ ID NO:223)

15 **Name:** Tx3.1

Species: textile

Cloned: Yes

20 **DNA Sequence:**

GGAACAGTCACCCCCACAGGCCAGCCAAGAGCAGACAGCCACAGCTACGTGAAGA
 AGGGTGGAGAGAGGGTTCATGATGTTGAAAATGGGAGTGGTGCTATTCATCTTCTGG
 TACTGTTCCCCTGGCAACGCTCCAGCTGGATGCAGATCAACCTGTAGAACGATATG
 CGGAGAACAAACAGCTCCTCAACCCAGATGAAAGGAGGGAAATCCTATTGCCTGCT
 CTGAGGAAGTTCTGCTGTGATTGAAATTGGTGCCACATTCTGGATTGTGAGTGCTGC
 TACGGTTAGCGCCGAACATCCATGGCACTGTGCTGGCGGTTCATCCAAACAACG
 ACAGCGTTGTTGATTCATGTATCATTCGGCCCACGTCTTGCTTAAGAATGACG
 AACATGATTGCACTCTGGTTCAGATTCTGTTCTTGACAATAAATGACAAAcC
 TCC (SEQ ID NO:224)

25 **Translation:**

MMLKMGVVLFIFLVLFPLATLQLDADQPVERYAENKQLNPDERREILLPALRKFCDS
 NWCHISDCECCYG (SEQ ID NO:225)

30 **Toxin Sequence:**

Phe-Cys-Cys-Asp-Ser-Asn-Xaa4-Cys-His-Ile-Ser-Asp-Cys-Xaa1-Cys-Cys-Xaa5-# (SEQ ID
 NO:226)

35 **Name:** U031

Species: textile

Isolated: Yes

Cloned: Yes

40 **DNA Sequence:**

CAAGGAACAGTCACCCCCACAGGCCAGCCAAGAGCAGACAGCCACAGCTACGTGA
 AGAAGGGTGGAGAGAGGGTTGTGATGTTGAAAATGGGAGTGGTGCTATTCATCTTC
 45 CTGGTACTGTTCCCCTGGCAACGCTCCAGCTGGATGCAGATCAACCTGTAGAACGA
 TATGCGGAGAACAAACAGCTCCTCAGCCCAGATGAAAGGAGGGAAATCATATTGCA
 TGCTCTGGGGACCGCGATGCTGTTCTGGGATGTGCGACCACCCAGTTGTACTTG

CTGCGGTTAGGCCAACATCCATGGCGCTGTGCTGGCGGTTTATCCCAACAAACG
 ACAGCGTTGTTGATTTCATGTATCATTGCGCCCACGTCTGTCTAAGAATGACG
 AACATGATTGCACTCTGGTTCAGATTCGTGTTCTTGACAATAATGACAAAAA
 CNCC (SEQ ID NO:227)

5

Translation:

MLKMGVVLFIFLVLFPLATLQLDADQPVERYAENKQLLSPDERREIILHALGTRCCSWD
 VCDHPSCTCCG (SEQ ID NO:228)

10

Toxin Sequence:

Cys-Cys-Ser-Xaa4-Asp-Val-Cys-Asp-His-Xaa3-Ser-Cys-Thr-Cys-Cys-# (SEQ ID NO:229)

Name: U032
Species: textile
Isolated: Yes
Cloned: Yes

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTGCTTCTGTTCCCC
 TTACTGCTCTTCCGCTGGATGGAGATCAACCCGCAGACCAAGCTGCAGAGCGTATG
 CAGGCCGAGCAGCATCCCTGTTGATCAGAAAAGACGGTGTGCAAGTTCCATG
 CCCCGATAGTTGCAGATATTGTGTTGCGGGTGATGATAACGTGTTGATGACCAACT
 TTCTCGAG (SEQ ID NO:230)

Translation:

GSMMMSKLGVLLTICLLFPLTALPLGDQPADQAAERMQAEQHPLFDQKRRCCKFPCP
 DSCRYLCCG (SEQ ID NO:231)

30

Toxin Sequence:

Arg-Cys-Cys-Lys-Phe-Xaa3-Cys-Xaa3-Asp-Ser-Cys-Arg-Xaa5-Leu-Cys-Cys-# (SEQ ID NO:232)

35

Name: T3.1
Species: tulipa
Cloned: Yes

DNA Sequence:

CGACCTCAAGAGGGATCGATAGCAGTTCATGTCTAAACTGGGAGTCTTGTGACAA
 TCTGTCTGCTTCTGTTCCCTTAUTGCTCTGCCGATGGATGGAGATGAACCTGCAG
 ACCGACCTGCAGAGCGTATGCAGGACAAACATTCTGAGCAGCATCCCTGTTG
 AGGAGAGACACGGATGTTGCAAGGGGCCGAAGGATGCTCCTCCAGAGAATGCAG
 ACCCCAAACATTGTTGCGGTCGACGATAACGTGTTGAGGGCCAACTTGTTATCACGG
 CTACGTCAAGTGTAGTGAATAAGTAAAATGATTGCAG (SEQ ID NO:233)

Translation:

MSKLGVLLTICLLFPLTALPMGDPEPADRPAERMQDNISSEQHPLFEERHGCKGPEG
CSSRECRPQHCCGRR (SEQ ID NO:234)

Toxin Sequence:

5 His-Gly-Cys-Cys-Lys-Gly-Xaa3-Xaa1-Gly-Cys-Ser-Ser-Arg-Xaa1-Cys-Arg-Xaa3-Gln-His-
Cys-Cys-# (SEQ ID NO:235)

10 **Name:** Fi3.1
Species: figulinus
Cloned: Yes

DNA Sequence:

15 CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCCTGCTGACCACATCT
GTCTGCTTCTGATTCCCCTTAAGTGCCTTCTTCGCTGGATGGAGATCAACCTGCAGACC
GACCTGCAGAGCGTATGCAGGATGGAATTCTATCTGAACACAGCATCCCATGTTGATC
CCGTCAGACGGTGTGCCGTGGCCATGCAACATAGGATGCGTACCTTGTGTTGAT
GACCAGTTTGTATCGCGGCCTCATCAAATGTCTAATGAATAAGTAAAACGATTGC
AGT (SEQ ID NO:236)

Translation:

20 MMSKLGVLLTICLLIPLTALS LDGDQPAD RPAERM QDG ISSEQHPMFDPV RRC CPWPC
NIGCVPCC (SEQ ID NO:237)

Toxin Sequence:

25 Cys-Cys-Xaa3-Xaa4-Xaa3-Cys-Asn-Ile-Gly-Cys-Val-Xaa3-Cys-Cys-^ (SEQ ID NO:238)

30 **Name:** Fi3.2
Species: figulinus
Cloned: Yes

DNA Sequence:

35 CAAGAGGGATCGATAGCAGTTCATGATGTTAAACTGGGAGTCCTGTTGACCACATCTG
TATGCTTCTGTTCCCTTACTGCTCTTCCGCTGGATGGAGAGCAACCTGCAGACCA
ACCTGCAGAGCGCATGCAGTATGACATGTTACGTGCAATGAATCCCTGGTTGATCC
CGTCAAAAGGTGCTGCTCGAAGAACTGCGCAGTATGCATCCCTGTTGCCGTAACT
GACCAGCTTGATTATCGCGGCCAAGGCTCTAATGAATAAGTAAAACGATTGCA GT
(SEQ ID NO:239)

Translation:

40 MMFKLGVL LTICML FPFT ALPLDGEQPA QPAERM QYDML RAMNPWFDPVKRCCSK
NCAVCIPCCP (SEQ ID NO:240)

Toxin Sequence:

45 Cys-Cys-Ser-Lys-Asn-Cys-Ala-Val-Cys-Ile-Xaa3-Cys-Cys-Xaa3-^ (SEQ ID NO:241)

5 **Name:** Fi3.3
Species: figulinus
Cloned: Yes

DNA Sequence:

10 CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGAGAGTCTTGTGACCTTATG
TCTGCTTCTGTTCCCCTACTGCTCTCCGCTGAATGAAGATCAACCTGCAGAGCGT
15 ATGCAGGACGACAATTCATCTGAGCAGCACCCCTGTATGACCACAAACGAAAGTG
TTGCCGGTGGCCATGCCCGCAAGATGCGGCTCTGTTGCCTGTAATAACGTGTTGG
20 CCAACTTGTTATCACGGCCACGTCAAATGTTAATGAATAAGTAAAACGATTGCAG
T (SEQ ID NO:242)

15 **Translation:**

20 MMSKLRVLLTLCLLFPLTALPLNEDQPAERMQDDNSSEQHPLYDHKRKCCRWPCTPAR
CGSCCL (SEQ ID NO:243)

25 **Toxin Sequence:**

30 Cys-Cys-Arg-Xaa4-Xaa3-Cys-Xaa3-Ala-Arg-Cys-Gly-Ser-Cys-Cys-Leu-^ (SEQ ID NO:244)

35 **Name:** Fi3.4
Species: figulinus
Cloned: Yes

40 **DNA Sequence:**

45 CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCTTATG
TCTGCTTCTGTTCCCCTGACTGCTCTCCGCTGGATGAAGATCAAGCTGCAGACCG
50 ACCTGCAGAGCGTATGCAGGGCATGTCATCTGAACAGCATCCCTCTTGATCCCGT
CAAACGGTGTGCGAGTTGTCACGCTGCCTGGATGCGTCCCTGTTGCACATCTTA
55 ATAACGTGTGGATGACCAACTGTGTTATCACGGCCACGTCAAGTGTCTAATGAATA
AGTAAAATGATTGCAGT (SEQ ID NO:245)

60 **Translation:**

65 MMSKLGVLVLLTLCLLFPLTALPLDEDQAADRPAERMQGMSSEQHPFFDPVKRCCELSR
CLGCVPCCTS (SEQ ID NO:246)

70 **Toxin Sequence:**

75 Cys-Cys-Xaa1-Leu-Ser-Arg-Cys-Leu-Gly-Cys-Val-Xaa3-Cys-Cys-Thr-Ser-^ (SEQ ID NO:247)

80 **Name:** Fi3.5
Species: figulinus
Cloned: Yes

85 **DNA Sequence:**

CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCTTATG
 TCTGCTTCTGTTCCCCTGACTGCTCTTCCGCTGGATGAAGATCAACCTGCAGACCG
 ACCTGCAGAGCGTATGCAGGGCATGTCATCTGAACAGCATCCCTCTTGATCCCCTG
 CAAACGGTGTGCGAGTTGTCAAAATGCCATGGATGCGTCCCTTGTGCATACCTTA
 5 ATAACGTGCGGATGACCAACTGTGTTATCACGGCCACGTCAAGTGTCTAATGAATA
 AGAAAAATGATTGCAGT (SEQ ID NO:248)

Translation:

MMSKLGVLTLCLLFPLTALPLDEDQPADRPAERMQGMSSEQHPFFDPVKRCCELSK
 10 CHGCVPCCIP (SEQ ID NO:249)

Toxin Sequence:

Cys-Cys-Xaa1-Leu-Ser-Lys-Cys-His-Gly-Cys-Val-Xaa3-Cys-Cys-Ile-Xaa3-[^] (SEQ ID NO:250)

15
Name: Qc3.2
Species: quercinus
Cloned: Yes

DNA Sequence:

CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTCGGAGTCTTGTGACCATCTG
 TCTGGTTCTGTTCCCCTAACAGCTCTCAGCTGGATGGAGATCAACCTGCAGACCG
 ACCTGCAGAGCGTACGCAGGACATTCTACAGAACAGTATCGAAAGTTGATCAGA
 GACAGAGGTGTGCCGGTGGCCATGCCCGTAGTTGCAGATGCTGCCATTACGTT
 AACGTGTTGGTGACCAGCTTGTATCACGACCACGCCAAGTGTCTAACGAATAAGT
 AAAATGATTGCAGT (SEQ ID NO:251)

Translation:

MMSKLGVLTLICLVLFPLTALQLGDQPADRPAERTQDISSEQYRKFDQRQRCCRWP
 30 PCP GSCRCCRYSR (SEQ ID NO:252)

Toxin Sequence:

Xaa2-Arg-Cys-Cys-Arg-Xaa4-Xaa3-Cys-Xaa3-Gly-Ser-Cys-Arg-Cys-Arg-Xaa5-Arg-[^]
 (SEQ ID NO:253)

35
Name: Qc3.3
Species: quercinus
Cloned: Yes

DNA Sequence:

CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCATCTG
 TCTGCTTCTGTTCCCCTACTGCTCTCCACTGGATGGAGATCAACCTGCAGATCAA
 TCTGCAGAGCGACCTGCAGAGCGTACGCAGGACACATTACAGCAGCATCCGTTATA
 40 TGATCCGAAAAGAAGGTGTGCCATTACCATGCCCGACAGCTGCCACGGATCTTG
 CTGCTATAAGTGATAACATGTTGATGGCCAGCTTGTATCACGGCCACGTCAAGTG
 TCTAATGAATAAGTAAAACGATTGCAGT (SEQ ID NO:254)

Translation:

MMSKLGVLLTICLLLFPALTALPLDGDQPADQSAERPAERTQDDIQQHPLYDPKRRCCRY
PCPDSCHGSCCYK (SEQ ID NO:255)

5

Toxin Sequence:

Arg-Cys-Cys-Arg-Xaa5-Xaa3-Cys-Xaa3-Asp-Ser-Cys-His-Gly-Ser-Cys-Cys-Xaa5-Lys-^ (SEQ ID NO:256)

10

Name: Wi3.1
Species: wittigi
Cloned: Yes

15

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTGCTTCTGTTCCCC
TTACTGCTCTCCGGTGGGTGGAGATCAGCCTGCAGACCGACTTGCAGAGCGTATGC
AGGACGACACTTCATCTGAGCAGCATCCCTTGAAAAGAGACTACCATCATGTTGC
GACTTTGAGAGGGCTTGCGTAGTACCAGCATGCATACGTACAGTGTGCACAGGA
TAACGTGTTGATGACCAACTTCTCGAG (SEQ ID NO:257)

20

Translation:
MMSKLGVLLTICLLLFPITALPVGGDQPADRLAERMQDDTSSEQHPFEKRLPSCCDFERL
CVVPACIRHQCTG (SEQ ID NO:258)

25

Toxin Sequence:

Leu-Xaa3-Ser-Cys-Cys-Asp-Phe-Xaa1-Arg-Leu-Cys-Val-Val-Xaa3-Ala-Cys-Ile-Arg-His-Gln-Cys-Cys-Thr-# (SEQ ID NO:259)

30

Name: bt3a
Species: betulinus
Isolated: Yes

35

Toxin Sequence:

Cys-Cys-Lys-Gln-Ser-Cys-Thr-Thr-Cys-Met-Xaa3-Cys-Cys-Xaa4-^ (SEQ ID NO:260)

40

Name: T3.2
Species: tulipa
Cloned: Yes

45

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACAATCTGTCTGCTTCTGTTCCCC
TTACTGCTCTGCCGATGGATGGAGATGAACCTGCAGACCGACCTGCAGAGCGTATG
CAGGACAAACATTTCATCTGAGCAGCATCCCTTGTGAGGAGAGACACGGATGTTG

CGAGGGGCCAAGGGATGCTCCTCCAGAGAACATTGTTGCGGTC
GACGATAACGTGTTGATGACCAACTNTCTCGAG (SEQ ID NO:261)

Translation:

MMSKLGVLITCLLFPLTALPMGDDEPADRPAERMQDNISSEQHPLFEERHGCEGPK
GCSSRECRPQHCCGRR (SEQ ID NO:262)

Toxin Sequence:

His-Gly-Cys-Cys-Xaa1-Gly-Xaa3-Lys-Gly-Cys-Ser-Ser-Arg-Xaa1-Cys-Arg-Xaa3-Gln-His-
Cys-Cys-# (SEQ ID NO:263)

Name: A3.5

Species: aurisiacus

Cloned: Yes

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTACTTCTGTTCCCC
TTACTGCTTTCCGATGGATGGAGATCAACCTGCAGACCAACCTGCAGATCGTATGC
AGGACGACATTCATCTGAGCAGTATCCCTGTTGATAAGAGACAAAAGTGTGCA
CTGGGAGGAAGGGGTATGCTCCGGCAAAGCATGCAAAATCTCAAATGTTGCTCT
GGACGATAACGTGTTGATGACCAACTTCTCGAN (SEQ ID NO:264)

Translation:

MMSKLGVLITCLLFPLTAFPMDGDQPADQPADRMQDDISSEQYPLFDKRQKCCTGR
KGSCSGKACKNLKCCSGR (SEQ ID NO:265)

Toxin Sequence:

Xaa2-Lys-Cys-Cys-Thr-Gly-Arg-Lys-Gly-Ser-Cys-Ser-Gly-Lys-Ala-Cys-Lys-Asn-Leu-Lys-
Cys-Cys-Ser-# (SEQ ID NO:266)

Name: Bt3.5

Species: betulinus

Cloned: Yes

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTGCTTCTGTTCCCC
TTACTGCTGTTCCGTTGGATGGAGATCAACCTGCAGACCAACCTGCAGAGCGTATGC
AGAACGAGCAGCATCCCTCGTTGATCAGAAAAGAAGGTGCTGCCGGTGGCCATGC
CCCAGTATATGCGGCATGGCTAGGTGTTGCTTCGTATGATAACGTGTTGATGACCA
ACTTTCTCGAG (SEQ ID NO:267)

Translation:

MMSKLGVLITCLLFPLTAVPLDGDQPADQPAERMQNEQHPSFDQKRRCCRWPCCPSIC
GMARCCFVMITC (SEQ ID NO:268)

Toxin Sequence:

Arg-Cys-Cys-Arg-Xaa4-Xaa3-Cys-Xaa3-Ser-Ile-Cys-Gly-Met-Ala-Arg-Cys-Cys-Phe-Val-Met-Ile-Thr-Cys-^ (SEQ ID NO:269)

5

Name: Bt3.6
Species: betulinus
Cloned: Yes

10

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGTGATCATCTGTCTGCTTCTGTTCCCC
 TTACTGCTGTTCCGCTGGATGGAGATCAGCCTGCAGAGCGTACGCAGATCGAGCAG
 CATCCCTTGTGTTGACCAGAAAAGAAGGTGTTGCCGGTGGCCATGCCAGTAGATG
 CGGCATGGCTAGGTGTTGCTCGTCATGATAACGTGTTGATGANCGACCTCTCNAG
 (SEQ ID NO:270)

15

20

25

30

35

Toxin Sequence:

Arg-Gly-Gly-Cys-Cys-Thr-Xaa3-Xaa3-Lys-Lys-Cys-Lys-Asp-Arg-Ala-Cys-Lys-Xaa3-Ala-Arg-Cys-Cys-Gly-Xaa3-# (SEQ ID NO:275)

40

45

Name: Pr3.2
Species: parius
Cloned: Yes

5 **DNA Sequence:**

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTGCTTCTGTTCCCC
 TTACTGCTCTTCCGATGGATGGTATCAACCTGCAGACCGACTTGTAGAGCGTATGC
 AGGACAACATTTCATCTGAGCAGCATCCCTCTTGAAAAGAGAAGAGGCTGTTGC
 ACACCTCCGAGGAAATGCAAAGACCGAGCCTGCAAACCTGCACGTTGTTGCCGCCC
 10 AGGATAACGTGTTGATGACCAACTTCTCGAG (SEQ ID NO:276)

15 **Translation:**

MMSKLGVLLTICLLLFPALTALPMGDQPADRLVERMQDNISSEQHPFFEKRRCGCTPPR
 KCKDRACKPARCCGPG (SEQ ID NO:277)

20 **Toxin Sequence:**

Arg-Gly-Cys-Cys-Thr-Xaa3-Xaa3-Arg-Lys-Cys-Lys-Asp-Arg-Ala-Cys-Lys-Xaa3-Ala-Arg-
 Cys-Cys-Gly-Xaa3-# (SEQ ID NO:278)

25 **Name:** Ct3.1
Species: coronatus
Cloned: Yes

30 **DNA Sequence:**

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTGCTTCTGTTCCAA
 TTACTGCCCTCCGCTGGATGAAGATCAACCTGCAGACCGACCTGCAGAGCGTATGC
 AGGACATTGCAACTGAACAGCATCCCTGTTGATCCCGTCAAACGGTGCTGCGATT
 GGCCATGCATCCCAGGATGCACCCCTGTTGCTGCCTGATAACGTGTTGATGACC
 AACTTCTCGAG (SEQ ID NO:279)

35 **Translation:**

MMSKLGVLLTICLLLFPITALPLDEDQPADRPAERMQDIATEQHPLFDPVKRCCDWPCIP
 GCTPCCLP (SEQ ID NO:280)

40 **Toxin Sequence:**

Cys-Cys-Asp-Xaa4-Xaa3-Cys-Ile-Xaa3-Gly-Cys-Thr-Xaa3-Cys-Cys-Leu-Xaa3-^ (SEQ ID
 NO:281)

45 **Name:** Ms3.1
Species: musicus
Cloned: Yes

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTGCTTCTGTTCTC
 TTTCTGCTCTTCCGATGGATGAAGATCAACTTGCAGACCTACCTGCAGAGCGTATGC

GGGACACTGCAACTGTAGATCATCCCTCCTATGATCCTGACAAAGCGTGCTGCGAG
 CAGAGCTGTACAACATGCTTCCGTGCTGCTAGCCTGAACACAGTAACGTGTTGAT
 GACCAACTTCTCGAG (SEQ ID NO:282)

5 Translation:

MMSKLGVLLTICLLLPLSALPMDEDQLADLPAERMRDTATVDHPSYDPDKACCEQSC
 TTCFPCC (SEQ ID NO:283)

Toxin Sequence:

10 Ala-Cys-Cys-Xaa1-Gln-Ser-Cys-Thr-Thr-Cys-Phe-Xaa3-Cys-Cys-^ (SEQ ID NO:284)

15 Name: bt3b
Species: betulinus
Isolated: Yes

Toxin Sequence:

Ala-Cys-Cys-Xaa1-Gln-Ser-Cys-Thr-Thr-Cys-Met-Xaa3-Cys-Cys-^ (SEQ ID NO:285)

Name: bt3c
Species: betulinus
Isolated: Yes

Toxin Sequence:

Cys-Cys-Xaa1-Gln-Ser-Cys-Thr-Thr-Cys-Met-Xaa3-Cys-Cys-Xaa4-? (SEQ ID NO:286)

30 Name: Pn3.2
Species: pennaceus
Cloned: Yes

DNA Sequence:

35 GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTGCTTCTGTTCCCC
 TTACTGCTCTCCGCTGGATGGAGATCAACCTGCATACCAAGCTGCAGAGCGTATGC
 AGGCCGAGCATCATCCCTTGTGATCAGAAAAGACGGTGCTGCAAGTTCCATGCC
 CCGATAGTTGCAAATATTGTGTTGCGGGTGATGATAACATGTTGATGACCAACTTT
 CTTGAG (SEQ ID NO:287)

40 Translation:

MMSKLGVLLTICLLLPLTALPLGDQPAYQAAERMQAEHHPLFDQKRRCCKFPCPDS
 CKYLCCG (SEQ ID NO:288)

45 Toxin Sequence:

Arg-Cys-Cys-Lys-Phe-Xaa3-Cys-Xaa3-Asp-Ser-Cys-Lys-Xaa5-Leu-Cys-Cys-# (SEQ ID NO:289)

Name: Pu3.2
Species: pulicarius
Cloned: Yes

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTGCTTGTGTTCCCC
 TTACTGCTCTTCCGATGGATGGTGATCAACTTGCAGACCGACTTGTAGAGCGTATGC
 AGGACAAACATTTCATCTGAGCAGCATCCCTCTTGATCCCGTCAAACGGTGTGCG
 TCAGCTGTTACATGGGATGCATCCCTGTTGCTCTAGTAATAACGTGTTGATGACC
 AACTTCTCGAG (SEQ ID NO:290)

Translation:

MMSKLGVLITICLLFPLTALPMGDQLADRLVERMQDNISSEQHPFFDPVKRCCVSCY
 MGCIPCCF (SEQ ID NO:291)

Toxin Sequence:

Cys-Cys-Val-Ser-Cys-Xaa5-Met-Gly-Cys-Ile-Xaa3-Cys-Cys-Phe-^ (SEQ ID NO:292)

Name: Pu3.3
Species: pulicarius
Cloned: Yes

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCCTGTCTGCTTGTGTTCCCC
 TTACTGCTCTTCCACTGGATGAAGATCAACTTGCAGACCGACCTGCAGAGCGTATGC
 AGGATGACACTTCAGCTGCACAGATTTCGGGTTGATCCCGTCAAACGGTGTGCA
 AATTGCTATGCTACTCGGGATGCACTCCTGTTGCCATATTGATAACGTGTTGATG
 ACCAACTTCTCGAG (SEQ ID NO:293)

Translation:

MMSKLGVLTVCLLCPPLTALPLDEDQLADRPAERMQDDTSAAQIFGFDPVKRCCCKLL
 CYSGCTPCCHI (SEQ ID NO:294)

Toxin Sequence:

Cys-Cys-Lys-Leu-Leu-Cys-Xaa5-Ser-Gly-Cys-Thr-Xaa3-Cys-Cys-His-Ile-^ (SEQ ID NO:295)

Name: Ra3.2
Species: rattus
Cloned: Yes

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTGCTTGTGTTCCGC
 TTACTGCTCTTCCGATGGATGGTGATCAACCTGCAGACCGACTTGTAGAGCGTATAAC

AGGACAACATTCTATCTGAGCAGCATCCCTTCTTGAAAAGAGAAGAGGCTGTTGC
GCACCTCCGAGGAATGCAAAGACCGAGCCTGCAACCTGCACGTTGCTGCAGGCC
AGGATAACGTGTTGATGACCAACTTCTCGAG (SEQ ID NO:296)

5 **Translation:**

MMSKLGVLLTICLLVFPLTALPMDQPADRLVERIQDNISSEQHPFFEKRRGCCAPPRK
CKDRACKPARCCGPG (SEQ ID NO:297)

Toxin Sequence:

10 Arg-Gly-Cys-Cys-Ala-Xaa3-Xaa3-Arg-Lys-Cys-Lys-Asp-Arg-Ala-Cys-Lys-Xaa3-Ala-Arg-
Cys-Cys-Gly-Xaa3-# (SEQ ID NO:298)

15 **Name:** Sm3.3

Species: *stercusmuscarum*

Cloned: Yes

20 **DNA Sequence:**

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACAATCTGTCTGCTTCTGTTCCCC
TTATTGCTCTTCCGCTGGATGGAGATCAACCTGCAGACCGACCTGCAGAGCGTATGC
AGGACGACATTCTATCTGAGAACGATCCCTGTTGATAAGAGACAAACGGTGTG
AATGGGCGGAGGGGATGCTCCAGCAGATGGTGCAGAGATCACTCACGTTGTTGCGG
TCGACGATAACGTGTTGATGACCAACTTCTCGAG (SEQ ID NO:299)

25 **Translation:**

MMSKLGVLLTICLLLFPPLIALPLDGDQPADRPAERMQDDISSEKHPLFDKRQRCCNGRR
GCSSRWCRDHSRCCGRR (SEQ ID NO:300)

Toxin Sequence:

30 Xaa2-Arg-Cys-Cys-Asn-Gly-Arg-Arg-Gly-Cys-Ser-Ser-Arg-Xaa4-Cys-Arg-Asp-His-Ser-Arg-
Cys-Cys-# (SEQ ID NO:301)

35 **Name:** Eb3.1

Species: *ebraeus*

Cloned: Yes

40 **DNA Sequence:**

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTGCTTCTGTTCCCC
TTACTGCTCTTCCACTGGATGAAGGTCAACCTGCAGACCTACCTGCAGAGCGTATGC
AGGACATTGCAACTGAACAGCATCCCTGTTGATCCTGTCACCGGTGTGCGAGC
AGCCATGCTACATGGGATGCATCCCTGTTGC TCTAATAATAACGTGTTGATGACC
AACTTCTCGAG (SEQ ID NO:302)

45 **Translation:**

MMSKLGVLLTICLLLFPPLALPLDEGQPADLPAERMQDIATEQHPLFDPVKRCCEQPCY
MGCIPCCF (SEQ ID NO:303)

Toxin Sequence:

Cys-Cys-Xaa1-Gln-Xaa3-Cys-Xaa5-Met-Gly-Cys-Ile-Xaa3-Cys-Cys-Phe-[^] (SEQ ID NO:304)

5

Name: Eb3.2
Species: ebraeus
Cloned: Yes

10

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTGCTTCTGTTCCCC
 TTACTGCTCTTCCACTGGATGAAGATCAACCTGCAGACCTACCTGCAGAGCGTATGC
 AGGACATTGCAACTGAACAGCATCCCTGTTGATCCTGTCAAACGGTGCTGCGCGC
 AGCCATGCTACATGGGATGCATCCCTGTTGCTTCTAATAATAACGTGTTGATGACC
 AACTTCTCGAG (SEQ ID NO:305)

15

Translation:

MMSKLGVLLTICLLLFPPLTALPLDEDQPADLPAERMQDIATEQHPLFDPVKRCCAQPCY
 MGCIPCCF (SEQ ID NO:306)

20

Toxin Sequence:

Cys-Cys-Ala-Gln-Xaa3-Cys-Xaa5-Met-Gly-Cys-Ile-Xaa3-Cys-Cys-Phe-[^] (SEQ ID NO:307)

25

Name: Fd3.2
Species: flavidus
Cloned: Yes

30

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTGCTTCTGTTCCCC
 TTACTGCTGTTCCGTTGGATGGAGATCAACCTGCAGACCCGCCTGCAGAGCGTATGC
 AGAACGAGCAGCATCCCTGTTGATCAGAAAAGAAGGTGCTGCCGGTGGCCATGC
 CCCAGTATATGCGGCATGGCTAGGTGTTGCTCGTCATGATAACGTGTTGATGACCAA
 CTTTCTCGAG (SEQ ID NO:308)

35

Translation:

MMSKLGVLLTICLLLFPPLAVPLDGDQPADQPAERMQNEQHPLFDQKRRCCRWPCPSIC
 GMARCCSS (SEQ ID NO:309)

40

Toxin Sequence:

Arg-Cys-Cys-Arg-Xaa4-Xaa3-Cys-Xaa3-Ser-Ile-Cys-Gly-Met-Ala-Arg-Cys-Cys-Ser-Ser-[^]
 (SEQ ID NO:310)

45

Name: Mf3.1
Species: miliaris
Cloned: Yes

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCTGCTTCTGTTCCAA
 TTACTGCCCTTCCACTGGATGAAGATCAACCTGCAGACCGACCTGCAGAGCGTATGC
 5 AGGACATTGCAACTGAACACAGCATCCCTGTTGATCCCCTCAAACCGGTGTTGCGATT
 GCCATGCAGCGCAGGATGCTACCCCTGTTGCTTCCCTTAATAACGTGTTGATGACC
 AACTNANGNAAAAAAA (SEQ ID NO:311)

Translation:

10 MMSKLGVLITICLLFPITALPLDEDQPADRPAERMQDIATEQHPLFDPVKRCCDWPCS
 AGCYPCCFP (SEQ ID NO:312)

Toxin Sequence:

Cys-Cys-Asp-Xaa4-Xaa3-Cys-Ser-Ala-Gly-Cys-Xaa5-Xaa3-Cys-Cys-Phe-Xaa3-^ (SEQ ID
 15 NO:313)

Name: Mf3.2
Species: miliaris
Cloned: Yes
Notes:

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTGGTGCCTTCGTTCTGGTCCTGTTCCCC
 TGGCAACACTCCAACGGATGCAGATCAACCTGCAGACCGACCTGCGCGTAAAAAG
 GGCATTGCAACTAACGGCATCCCTGCTGATCCTGTCAGAGGGTGTGCCCTCCA
 ATGTGCACACCAGCTCCCTGCTGTTGTTGTTAATAACGTGTTGATGNATGATGN
 AN (SEQ ID NO:314)

Translation:

30 MMSKLGVPVFVLFPLATLQLDADQPADRPARKGIATKRHPLSDPVRGCCPPMCTPCFPCC
 FR (SEQ ID NO:315)

Toxin Sequence:

35 Gly-Cys-Cys-Xaa3-Xaa3-Met-Cys-Thr-Xaa3-Cys-Phe-Xaa3-Cys-Cys-Phe-Arg.^ (SEQ ID
 NO:316)

Name: Af3.1
Species: ammiralis
Cloned: Yes

DNA Sequence:

40 CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCATCTG
 TCTGCTTCTGTTCCCTTACTGCTCTCCGCTGGATGGAGATCAACCTGCAGACCCA
 45 AGCTGCAGAGCGTATGCAGGCCGAGCAGCATCCCTGTTGATCAGAAAAGACGGT
 GTTGCAGGTTCCATGCCCGATACTTGCAAGACATTGTGTTGCGGGTGATGATAAC

GTGCTGATGACCCACTTGTACACGGCTACGTCAAGTGTCTAATGAATAAGTAAA
ATGATTGCAGT (SEQ ID NO:317)

Translation:

5 MMSKLGVLLTICLLLPLTALPLDGDQPADQAAERMQAEQHPLFDQKRRCCRFPCPDT
CRHLCCG (SEQ ID NO:318)

Toxin Sequence:

10 Arg-Cys-Cys-Arg-Phe-Xaa3-Cys-Xaa3-Asp-Thr-Cys-Arg-His-Leu-Cys-Cys-# (SEQ ID
NO:319)

15 **Name:** Af3.2

Species: ammiralis

Cloned: Yes

DNA Sequence:

20 CAAGAGGGATCGATAGCAGTTCATGATGTTAAACTGGGAGTCTTGCTGACCATCTG
TCTACTTCTGTTTCCCTTAATGCTGTTCCGCTGGATGGAGATCAACCTGCAGACCA
25 ACCTGCAGAGCGTCTGCTGGACGACATTTCATCTGAAAATAATCCCTTATGATCC
GCCCAAACGGTGTGCATGACTTGCTTCGGTTGCACACCTGTTGGATGACCAGC
CTCATCAAGTGTCTAACGAATAAGTAAAACGATTGCAGT (SEQ ID NO:320)

Translation:

25 MMFKLGVLLTICLLLFSLNAVPLDGDQPADQPAERLLDDISSENNPFYDPAKRCCMTCF
GCTPCCG (SEQ ID NO:321)

Toxin Sequence:

30 Cys-Cys-Met-Thr-Cys-Phe-Gly-Cys-Thr-Xaa3-Cys-Cys-# (SEQ ID NO:322)

35 **Name:** Af3.3

Species: ammiralis

Cloned: Yes

DNA Sequence:

40 CAAGAAGGATCGATAGCAGTTCATGATGTCATAACTGGGAGCCTGTTGACCATCT
GTCTACTTCTGTTTCCCTACTGCTGTTCCGCTGGATGGAGATCAACATGCAGACCA
AACCTGCAGAGCGTCTGCAGGACCGCCTCCAAGTAAAATCATCCCTATATGATC
CCGTCAAACGGTGTGCATGATTGGAATGCGACTATTCTGCTGGCCTGCTGTA
TTTTTCATAACCTTGTATCGCGGCCTCATCCTAGTGTCAAATGAATAAGTAAAA
CGATTGCAGT (SEQ ID NO:323)

Translation:

45 MMSKLGALLTICLLLFSLTAVPLDGDQHADQPAERLQDRLPTENHPLYDPVKRCCDDSE
CDYSCWPCCIFS (SEQ ID NO:324)

Toxin Sequence:

Cys-Cys-Asp-Asp-Ser-Xaa1-Cys-Asp-Xaa5-Ser-Cys-Xaa4-Xaa3-Cys-Cys-Ile-Phe-Ser-^ (SEQ ID NO:325)

5

Name: Af3.4
Species: ammiralis
Cloned: Yes

10

DNA Sequence:

CAAGAGGGATCGATAGCAGTTCATGATGTTAAACTCGGAGTCTGCTGACCATCTG
 TCTACTTCTGTTCCCTAAAtGCTGTTCCGCTGGATGGAGATCAACATGCAGACCAA
 CCTGCAGAGCGTCTGCAGGACCGCCTCCAActGAAAATCATCCCTTATATGATCCC
 GTCAAACGGTGTGCAGGTTGTTATGCCTCAGTTGCAACCCCTGTTGGATGACCA
 GCTTGTTATCACGGCCTCATCAAGTGTCTAATGAATAAGTAAAACGATTGCAGT
 (SEQ ID NO:326)

15

Translation:

MMFKLGVLLTICLLLFSLIAVPLDGDQHADQPAERLQDRLPTENHPLYDPVKRCCRLLC
 LSCNPCCG (SEQ ID NO:327)

20

Toxin Sequence:

Cys-Cys-Arg-Leu-Leu-Cys-Leu-Ser-Cys-Asn-Xaa3-Cys-Cys-# (SEQ ID NO:328)

25

Name: Af3.6
Species: ammiralis
Cloned: Yes

30

DNA Sequence:

CAAGAAGGATCGATAGCAGTTCATGATGTTAAACTGGGAGCCTGTTGACCATCT
 GTCTACTTCTGTTCCCTTACTGCTGTTCCGCTGGATGGAGATCAACATGCAGACCC
 AACCTGCAGAGCGTCTGCAGGACCGCATTCCAActGAAGATCATCCCTTATTGATC
 CCAACAAACGGTGTGCGATGATTGGAATGCGGCTATTCATGCTGGCCTGCTGTT
 ATGGATAAGCTTGTATCGCGGCCTCATCCAGTGTCAACGAATAAGTAAAACGATT
 GCAGT (SEQ ID NO:329)

35

Translation:

MMSKLGALLTICLLLFSLTAVPLDGDQHADQPAERLQDRIPTEDHPLFDPNKRCCDDSE
 CGYSCWPCCYG (SEQ ID NO:330)

40

Toxin Sequence:

Cys-Cys-Asp-Asp-Ser-Xaa1-Cys-Gly-Xaa5-Ser-Cys-Xaa4-Xaa3-Cys-Cys-Xaa5-# (SEQ ID NO:331)

45

Name: Sf3.1
Species: spurius
Cloned: Yes

5 DNA Sequence:

CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTGCTGACCAC
 GTCTGCTTCTGTTCCACGTACTTCTCTTCCGCTGGATGGAGATCAACCTGCAGTC
 ATCTGCAAAGCGTATGCATTCATCTACAGCGTCGTTCTTGATCCCCTCAAACG
 GTGTTGCCCTAGATGCAGCGAGTGCAACCCCTGTTGGATGACCAGCTTGTAC
 10 GCGGCCTCATTAAAGTGTCTAATGAATAAGTAAAATGATTGCAGT (SEQ ID NO:332)

Translation:

MMSKLGVLITICLLLFPRTSLPLGDQPAVRSAKRMHSSIQRFFDPVKRCCPRCSECNP
 CCG (SEQ ID NO:333)

15 Toxin Sequence:

Cys-Cys-Xaa3-Arg-Cys-Ser-Xaa1-Cys-Asn-Xaa3-Cys-Cys-# (SEQ ID NO:334)

20 Name: Om3.1
Species: omaria
Cloned: Yes

DNA Sequence:

25 CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTCGTTGACCAC
 GTCTACTTCTATTTCCTTACTGCTGTTCCGCTTGATGGAGATCAACATGCAGACCA
 ACCTGCAGAGCGTCTGCAGGGCGACATTATCTGAAAAGCATCCCTATTAAATCC
 CGTCAAACGGTGTGCGATGAGGAAGAACATGCAGCAGTGCATGCTGGCCTGTTGTT
 GGGGGTGATCAGCTTGTATCGCGGCCTCATCAAGTGTCTAATGAATAAGTAAAAT
 30 GATTGCAGT (SEQ ID NO:335)

Translation:

MMSKLGVSLLTICLLLFSLTAVPLGDQHADQPAERLQGDILSEKHPLFNPVKRCCDEEE
 CSSACWPCCWG (SEQ ID NO:336)

35 Toxin Sequence:

Cys-Cys-Asp-Xaa1-Xaa1-Xaa1-Cys-Ser-Ser-Ala-Cys-Xaa4-Xaa3-Cys-Cys-Xaa4-# (SEQ ID NO:337)

40 Name: Om3.2
Species: omaria
Cloned: Yes

45 DNA Sequence:

CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTGTTGATCATCTG
 TCTACTTCTGTGTCCTTACTGCTGTTGGAGGATGGAGATCAACCTGCAGACCG

ACCTGCAGAGCGTATGCAGGACGACATTCAACTGAGCATCATCCCTTTATGATCC
 CGTCAAACGGTGTGCAAGTACGGGTGGACATGCTGCTAGGATGCACTCCTGTGA
 TTGTTGACCAGTTTGTATCGCGCCTCGTCAAGTGTCTAATGAATAAGTAAAACG
 ATTGCAGT (SEQ ID NO:338)

5

Translation:

MMSKLGVLLIICLLCPLTAVLEDGDQPADRPAERMQDDISTEHHPFYDPVKRCCKYG
 WTCLLGCTPCDC (SEQ ID NO:339)

10

Toxin Sequence:

Cys-Cys-Lys-Xaa5-Gly-Xaa4-Thr-Cys-Leu-Leu-Gly-Cys-Thr-Xaa3-Cys-Asp-Cys-[^] (SEQ ID NO:340)

15

Name: Om3.3
Species: omaria
Cloned: Yes

20

DNA Sequence:

CAAGAGGGATCGATAGCAGTTCATGATGTCTATACTGGGAGTCTTGTGATCATCTG
 TCTACTTCTGTGTCCTTACTGCTGTTCTGGAGGATGGAGATCAACCTGCAGACCG
 ACCTGCAGAGCGTATGCAGGACGGCATTTCATCTGAACATCATCCCTTTGGATCC
 CGTCAAACGGTGTGCCATCTATTGGCATGCCGCTTGGATGCTCGCCTTGTGTTG
 GTGACCAGCTTGTATCGCGCCTCATCAAGTGTCTAATGAATAAGTAAAACGATT
 GCAGT (SEQ ID NO:341)

25

Translation:

MMSILGVLLIICLLCPLTAVLEDGDQPADRPAERMQDGISSEHHPFLDPVKRCCCHLLAC
 RFGCSPCCW (SEQ ID NO:342)

30

Toxin Sequence:

Cys-Cys-His-Leu-Leu-Ala-Cys-Arg-Phe-Gly-Cys-Ser-Xaa3-Cys-Cys-Xaa4-[^] (SEQ ID NO:343)

35

Name: Om3.4
Species: omaria
Cloned: Yes

40

DNA Sequence:

CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGATCATCTG
 TCTACTTCTTGTCCTTACTGCTGTTCCGCAGGATGGAGATCAACCTGCAGACCG
 ACCTGCAGAGCGTATGCAGGGCGGCATTTCATCTGAACATCATCCCTTTGGATCC
 CGTCAAACGGTGTGCAGGTACGGGTGGACATGCTGGCTAGGATGCACTCCCTGTG
 GTTGTGACCAGCTTGTATCGCGCCTCATCAAGTGTCTAATGAATAAGTAAAAC
 GATTGCAGT (SEQ ID NO:344)

45

Translation:

MMSKLGVLLIICLLLPLTAVPQDGDPADPRAERMQGGISSEHPFFDPVKRCCRYGW
TCWLGCCTPCGC (SEQ ID NO:345)

Toxin Sequence:

Cys-Cys-Arg-Xaa5-Gly-Xaa4-Thr-Cys-Xaa4-Leu-Gly-Cys-Thr-Xaa3-Cys-Gly-Cys-^ (SEQ ID NO:346)

10 **Name:** Ep3.1
Species: episcopatus
Cloned: Yes

DNA Sequence:

15 CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCATCTG
TCTACTTCTGTTCCCTTATTGCTGTTCCGCTTGATGGAGATCAACATGCAGACCAA
CCTGCAGAGCGTCTGCAGGGCGACATTTATCTGAAAAGCATCCCTATTATGCCT
GTCAAACGGTGTGCGATGAGGACGAATGCAACAGTTCATGCTGGCCTGTTGG
GGGTGATCAGCTTGTATCGCGGCCTGATCAAGTGTATAATGAATAAGTAAAACG
ATTGCAGT (SEQ ID NO:347)

Translation:

MMSKLGVLLTICLLLFSLIAVPLDGDQHADQPAERLQGDILSEKHPLFMPVKRCCDEDE
CNSSCWPCCG (SEQ ID NO:348)

20 **Toxin Sequence:**

Cys-Cys-Asp-Xaa1-Asp-Xaa1-Cys-Asn-Ser-Ser-Cys-Xaa4-Xaa3-Cys-Cys-Xaa4-# (SEQ ID NO:349)

30 **Name:** Ep3.2
Species: episcopatus
Cloned: Yes

DNA Sequence:

35 CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCATCTG
TCTACTTCTGTTCCCTTATTGCTGTTCCGCTTGATGGAGATCAACATGCAGACCAA
CCTGCAGAGCGTCTGCAGGGCGACATTTATCTGAAAAGCATCCCTATTATGCCT
GTCAAACGGTGTGCGATGAGGACGAATGCAAGCAGTTCATGCTGGCCTGTTGG
GGATGAGCAGCTTGTATCGCGGCCTCATCAAGTGTATAATGAATAAGTAAAACG
ATTGCAGT (SEQ ID NO:350)

Translation:

MMSKLGVLLTICLLLFSLIAVPLDGDQHADQPAERLQGDILSEKHPLFMPVKRCCDEDE
CSSSCWPCCWG (SEQ ID NO:351)

45 **Toxin Sequence:**

Cys-Cys-Asp-Xaa1-Asp-Xaa1-Cys-Ser-Ser-Cys-Xaa4-Xaa3-Cys-Cys-Xaa4-# (SEQ ID NO:352)

5 **Name:** Ep3.3
Species: episcopatus
Cloned: Yes

DNA Sequence:

10 CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCATCTG
TCTACTTCTGTTTCCCTTACTGCTGTTCCGCTTGATGGAGATCAACATGCAGACCAA
CCTGCAGAGCGTCTGCAGGGCGACATTATCTGAAAAGCATCCCTATTAATCCC
GTCAAACGGTGTGCCCGCGCGCATGTGCCATGGGATGCAAGCCTTGTGG
ATGAGCAGCTTGTATCGTGGCCTCATCAAGTGTCTAATGAATAAGTAAAACGATT
15 GCAGT (SEQ ID NO:353)

Translation:

MMSKLGVLLTICLLLFSLTAVPLDGDQHADQPAERLQGDILSEKHPLFNPVKRCCPAAA
CAMGCKPCCG (SEQ ID NO:354)

Toxin Sequence:

Cys-Cys-Xaa3-Ala-Ala-Ala-Cys-Ala-Met-Gly-Cys-Lys-Xaa3-Cys-Cys-# (SEQ ID NO:355)

25 **Name:** Au3.2
Species: aulicus
Cloned: Yes

DNA Sequence:

30 CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCATCTG
TCTGCTTCTGTTTCCGTTACTGCTCTTCCGCCGGATGGAGATCAACCTGCAGACCG
AGCTGCAGAGCGTAGGCAGGTCGAGCAGCATTCCGTGTTGATCATGAAAGAGGGT
GTTGCTCGCCACCATGCCACAGTATTGCGCTGCTTCTGTTGCCGGGTGATGATAAC
GTGTTGATGACCCACTTGTATCACGGCTGCGTCAAGTGTCTAATGAATAAGTAAA
35 ATGATTGCAGT (SEQ ID NO:356)

Translation:

MMSKLGVLLTICLLLFSVTALPPDGDQPADRAAERRQVEQHPVFDHERGCCSPPCHSIC
AAFCCG (SEQ ID NO:357)

Toxin Sequence:

Gly-Cys-Cys-Ser-Xaa3-Xaa3-Cys-His-Ser-Ile-Cys-Ala Ala-Phe-Cys-Cys-# (SEQ ID NO:358)

40 **Name:** Au3.3
Species: aulicus
Cloned: Yes

DNA Sequence:

CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCATCTG
 TCTACTTCTGTTCCCTTACTGCTGTCGCTTGATGGAGATCAACATGCAGACCAA
 5 CCTGCAGAGCGTCTGCAGGGCGACATTATCTGAAAAGCATCCCTATTAATCCC
 GTCAAACGGTGTGCCGACCGGTGGCATGTGCCATGGGATGCAAGCCTTGTGTTGG
 ATGAGCAGCTTGTATCGTGGCCTCATCAAGTGTCTAATGAATAAGTAAAATGATT
 GCAGT (SEQ ID NO:359)

Translation:

MMSKLGVLLTICLLLFSLTAVPLDGDQHADQPAERLQGDILSEKHPLFNPVKRCCRPVA
 CAMGCKPCCG (SEQ ID NO:360)

Toxin Sequence:

Cys-Cys-Arg-Xaa3-Val-Ala-Cys-Ala-Met-Gly-Cys-Lys-Xaa3-Cys-Cys-# (SEQ ID NO:361)

Name: Au3.4
Species: aulicus
Cloned: Yes

DNA Sequence:

CAAGAGGGATCGATAGCAGTTCaTGATGTCTAAACTGGGAGTCTTGTGATCATCTG
 TCTACTTCTGCTCCCTTACTGCTGTCGCTGGATGGAGATCAACCTGCAGACCG
 20 ACCTGCAGAGCGTATGCAGGACGACATTCTCATCTGAACATCAACCCATGTTGATGC
 CATCAGACAGTGTGCCCCGGCGGTGGCATGCCATGGGATGCGAGCCTTGTGTTG
 GATGACCAGCTTGTATCGCGGCCTCATCAAGTGTCTAATGAATAAGTAAAATGAT
 TGCAGT (SEQ ID NO:362)

Translation:

MMSKLGVLLIICLLSPLTAAPLDGDQPADRPAERMQDDISSEHQPMFDAIRQCCPAVA
 CAMGCEPCCG (SEQ ID NO:363)

Toxin Sequence:

Xaa2-Cys-Cys-Xaa3-Ala-Val-Ala-Cys-Ala-Met-Gly-Cys-Xaa1-Xaa3-Cys-Cys-# (SEQ ID NO:364)

Name: Ae3.1
Species: aureus
Cloned: Yes

DNA Sequence:

CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGCCTTGTGACCATCT
 45 GTCTACTTCTGTTCCCTTACTGCTGTCGCTGGATGGAGATCAACATGCAGACCC
 AACATGCAGAGCGTCTGCATGACCGCCTCCAATGAAAATCATCCCTATATGATC
 CCGTCAAACGGTGTGCGATTCGGAATGCGACTATTCTGCTGGCCTTGCTGTA

TTTTGGATAACCTTGTATCGCGCCTCATCAAGTGTCAAATGAATAAGTAAAAC
GATTGCAGT (SEQ ID NO:365)

Translation:

5 MMSKLGALLTICLLLFSLTAVPLDGDQHADQHAERLHDRLPENHPLYDPVKRCCDDS
ECDYSCWPCCIFG (SEQ ID NO:366)

Toxin Sequence:

10 Cys-Cys-Asp-Asp-Ser-Xaa1-Cys-Asp-Xaa5-Ser-Cys-Xaa4-Xaa3-Cys-Cys-Ile-Phe-# (SEQ ID
NO:367)

15 Name: Ae3.2

Species: aureus

Cloned: Yes

DNA Sequence:

CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGCCTTGTGACCATCT
GTCTACTTCTGTTTCCCCTAACTGCTGTTCCGCTGGATGGAGATCAACATGCAGACC
AACCTGCAGAGCGTCTGCAGGACCGCATTCCAAC TGAAAATCATCCCTTATTGATC
CGAACAAACGGTGTGCAATGATTGGAAATGCGACGATT CATGCTGGCCTGCTGTT
ATGGATAACCTTGTTATCGCGGCCATCAAGTGTCAAATGAATAAGTAAAACGAT
TGCAGT (SEQ ID NO:368)

Translation:

MMSKLGALLTICLLLFSLTAVPLDGDQHADQPAERLQDRPTENHPLFDPNKRCCNDWE
CDDSCWPCCYG (SEQ ID NO:369)

Toxin Sequence:

30 Cys-Cys-Asn-Asp-Xaa4-Xaa1-Cys-Asp-Asp-Ser-Cys-Xaa4-Xaa3-Cys-Cys-Xaa5-# (SEQ ID
NO:370)

35 Name: Cn3.1

Species: consors

Cloned: Yes

DNA Sequence:

CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCATCTG
40 TTTGCTCTGTTCCCCTACTGCTCTCCAATGGATGGAGATCAATCTGTAGACCGA
CCTGCAGAGCGTATGCAGGACGACATTCACTGAGCTGCATCCCTTGTCAATCAG
AAAAGAATGTGTTGGCGAAGGTGCGCCATGCCAGCTATTCAAGAACAGTCA
GATTGTCATTGTTAAATGACAACGTGTCGATGACCAACTCGTTATCACGACT
AATGAATAAGTAAAATGATTGCAGT (SEQ ID NO:371)

45

Translation:

MMSKLGVL LTICLLLFP LTAL PMDGDQ SVDR PAER MQDDIS SELHPL FNQ KRMCC GEG
APCP SYFR NSQ ICHCC (SEQ ID NO:372)

Toxin Sequence:

5 Met-Cys-Cys-Gly-Xaa1-Gly-Ala-Xaa3-Cys-Xaa3-Ser-Xaa5-Phe-Arg-Asn-Ser-Gln-Ile-Cys-His-Cys-Cys-^ (SEQ ID NO:373)

10 **Name:** Cn3.3

Species: consors

Cloned: Yes

DNA Sequence:

15 TAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACC ATCTG
TCTGCTTCTGTTCCCCTTATTGCTCTCCAATGGATGGAGATCAACCTGCAGACCGA
CCTGCAGAGCGTATGCAgGACGACATT CATCTCAGCAGCATCCCTTGTGATAAG
AGAGGCCGCTGTTGCGATGTGCCGAACGCATGCTCCGGCAGATGGTGCAGAGATCA
CGCACAA TGTGCGGATGACGATAACGTGTTGATGACCAACTTGTGATCACGGCTA
CATCAAGTGAATAAGTAAAACGATTGCAGT (SEQ ID NO:374)

Translation:

20 MMSKLGVL LTICLLLFP LIAL PMDGDQ PADR PAER MQDDISS QQHPL FDKR GRCC DV PN
ACSG RW CRD HA QCCG (SEQ ID NO:375)

Toxin Sequence:

25 Gly-Arg-Cys-Cys-Asp-Val-Xaa3-Asn-Ala-Cys-Ser-Gly-Arg-Xaa4-Cys-Arg-Asp-His-Ala-Gln-Cys-Cys-# (SEQ ID NO:376)

30 **Name:** Cn3.4

Species: consors

Cloned: Yes

DNA Sequence:

35 CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACTGTCTG
TTTGCTTCTGTTCCCCTTACTGCTCTCCGATGGATGGAGATCAACCTGCAGACCAA
CCTGCAGAGCGTATGCAGGACGACATT CATCTGAGCAGCATCCCTTGTGATAAG
AGACAAAGGTGTTGCACTGGGAAGAAGGGGTATGCTCCGGTAAAGCATGCAAAA
GTCTCAAATGTTGCTCTGGACGATAACGTGTTGATGACCAACTTGTATCACGGCT
40 ACGTCAAGTGTCTAGTGAATAAGTAAAACGATTGCAGT (SEQ ID NO:377)

Translation:

45 MMSKLGVL TVCLLFP LTAL PMDGDQ PADQ PAER MQDDIS SEQ HPL FDKR QRCC TGK
KGCS SGKACKSLKCCSGR (SEQ ID NO:378)

Toxin Sequence:

Xaa2-Arg-Cys-Cys-Thr-Gly-Lys-Ser-Cys-Ser-Gly-Lys-Ala-Cys-Lys-Ser-Leu-Lys-Cys-Cys-Ser-# (SEQ ID NO:379)

5 **Name:** Em3.1
Species: emaciatus
Cloned: Yes

DNA Sequence:

10 CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTGACCATCTGTCCTGTTCTGTT
TCCCCTTAAGTGTCTTCCGATGGATGGAGATCAACCTGCAGACCTACCTGCATTGCGTGCGCAGTTCTT
TGCACCTGAACATAGTCCCCGGTTGACCCCGTCAAACGGTGCTGCTCGCGGGATTGAGTGTGTTGCAT
CCCTGTTGCCCGTATGGATCACCTGATTATTGCGGCCACGTCAAGTGTCTAATGAATAAGTAAAATG
ATTGCAGT (SEQ ID NO:380)

15 **Translation:**

MMSKLGVLLTICLLLFPPLTVLPMDGDQPADLPALRAQFFAPEHSPRFDPVKRCCSRDCSVCIPCCPYGSP
(SEQ ID NO:381)

20 **Toxin Sequence:**

Cys-Cys-Ser-Arg-Asp-Cys-Ser-Val-Cys-Ile-Xaa3-Cys-Cys-Xaa3-Xaa5-Gly-Ser-Xaa3-^ (SEQ
ID NO:382)

25 -----
Where:

Xaa1 is Glu or γ -carboxy-Glu

Xaa2 is Gln or pyro-Glu

Xaa3 is Pro or hydroxy-Pro

30 Xaa4 is Trp or bromo-Trp

Xaa5 is Tyr, 125 I-Tyr, mono-iodo-Tyr, di-iodo-Tyr, O-sulpho-Tyr or O-phospho-Tyr

^ is free carboxyl or amidated C-terminus, preferably free carboxyl

is free carboxyl or amidated C-terminus, preferably amidated

? = Status of C-term not known.

35 TABLE2

Alignment of μ -Conopeptides (SEQ ID NO:)

TYPE 1

40	A3.4 (F283)	---CCKVQ-CES--C---TPCC^ (383)
	Ak3.1 (F585)	---CCELP-CG^GFC---VPCC^ (384)
	Ar3.1	---CCERP-CNIG-C---VPCC^ (385)
	Bn3.1 (F586)	---CCNWP-CSMG-C---IPCCYY^ (386)
	Bt3.1	---CCELP-CH-G-C---VPCCWP^ (387)
45	Bt3.2	---CCGLP-CN-G-C---VPCCWPS^ (388)
	Bt3.3	---CCSRN-CAV--C---IPCCPNWPA^ (389)
	bt3a	---CCKQS-CTT--C---MPCCW^ (390)

	bt3b	--ACCXQS-CTT---C---MPCC^ (391)
	bt3c	--CCEQS-CTT---C---MPCCW? (392)
	Ca3.3	R--CCRYP-CPDS-C--HGSCCYK^ (393)
	Ca3.4	--CCPPVACNMG-C---KPCC# (394)
5	Ca3.5	--CCDDSECDYS-C---WPCCMF# (395)
	Ca3.6 (F349)	--CCRR--CYMG-C---IPCCF^ (396)
	Circling	--CCPPVACNMG-C---KPCCG^ (397)
	Comatose/Death	SKQCCHLAACRFG-C---TOCCN^ (398)
	Cp3.1 (F594)	S---CCR--DCGED-C---VGCCR^ (399)
10	Ct3.1 (Z726)	--CCDWp-CIPG-C---TPCCLP^ (400)
	Da3.1	--CCDDSECDYS-C---WPCCILS^ (401)
	Da3.2	Z-QCCPPVACNMG-C---EPCC# (402)
	Da3.3	--CCNAGFCRFG-C---TPCCW^ (403)
	Di3.1	Z--CCVHP-C-P---C---TPCCR^ (404)
15	Fi3.1	--CCPWP-CNIG-C---VPCC^ (405)
	Fi3.2	--CCSKN-CAV---C---IPCCP^ (406)
	Fi3.3	--CCRWP-CP-ARC---GSCCL^ (407)
	Fi3.4	--CCELSRCL-G-C---VPCCTS^ (408)
	Fi3.5	--CCELSKCH-G-C---VPCCIP^ (409)
20	Ge3.1 (F590)	Z---CCTF--CNFG-C---QPCCVP^ (410)
	Ge3.2 (F343/Z734)	Z---CCTF--CNFG-C---QPCCLT^ (411)
	Ge3.3 (F590)	Z---CCTF--CNFG-C---QPCCVP^ (412)
	Gm3.1	--CCDDSECDYS-C---WPCCMF# (413)
	Gm3.2	G---CCHLLACRFG-C---SPCCW^ (414)
25	Gm3.3	--CCSWDVCDHPSC---T-CCG# (415)
	La3.1	--CCDWp-CS-G-C---IPCC^ (416)
	Lp3.1 (F340)	ZINCCPWP-CPST-C--RHQCCH^ (417)
	Lv3.1 (F341)	ZINCCPWP-CPDS-C--HYQCCH^ (418)
	Mr3.2	--CCRLS-CGLG-C---HPCC# (419)
30	Mr3.3	--ECCGSFACRFG-C---VPCCV^ (420)
	Mr3.4	SKQCCHLPACRFG-C---TPCCW^ (421)
	Mr3.5 (F286)	-MGCCPFP-CKTS-C--TTLCC# (422)
	Ms3.1 (Z738)	--ACCEQS-CTT---C---FPCC^ (423)
	Nb3.1 (F87)	--CCELP-CGPGFC---VPCC^ (424)
35	Pu3.1 (F339)	--CCN-S-CYMG-C---IPCCF^ (425)
	Qc3.1 (F342)	ZR-CCQWP-CPGS-C----RCCRT# (426)
	Qc3.2	ZR-CCRWP-CPGS-C----RCCRYR^ (427)
	Qc3.3	R--CCRYP-CPDS-C--HGSCCYK^ (428)
	QcIIIA	--CCSQD-CLV---C---IOCCPN# (429)
40	QcIIIB	--CCSRH-CWV---C---IOCCPN? (430)
	Ra3.1 (F351)	Z-TCCS-N-CGED-C---DGCCQ^ (431)
	Scratcher I	--CCR-T-C-FG-C---TOCC# (433)
	Ts3.1 (F592)	--CCH-K-CYMG-C---IPCCI^ (434)
	Ts3.2 (F345)	K--CCRPP-CAMS-C-GMARCCY^ (435)
45	Bt3.5 (Z495)	R--CCRWP-CPSI-C-GMARCCFVMITC^ (436)
	Bt3.6 (Z497)	R--CCRWP-CP-SRC-GMARCCFVMITC^ (437)
	Tx3.1	F--CCDSNWCHISDC----ECCY# (438)

	U014	--CCHWNWCDHL-C---SCCGS^ (439)
	U017	--DCCOLPACPFG-C---NOCC# (440)
	U019	--CCAPSACRLG-C---ROCCR^ (441)
5	U020	--CCAOSACRLG-C---ROCCR^ (442)
	U022	--CCAPSACRLG-C---RPCCR^ (443)
	U024	--GCCGSFACRFG-C---VOCCV^ (444)
	U031	--CCSWDVCDHPSC---TCC# (445)
	U032 (F353)	R--CCKFP-CPDS-C--RYLCC# (446)
10	Ae3.1	--CCDDSECDYS-C---WPCCIF# (447)
	Ae3.2	--CCNDWECDDS-C---WPCCY# (448)
	Af3.1	R--CCR-FPCPDT-C---RHLCC# (449)
	Af3.2	--CC--MTC-FG-C---TPCC# (450)
	Af3.3	--CCDDSECDYS-C---WPCCIFS^ (451)
15	Af3.4	--CCR-LLC-LS-C---NPCC# (452)
	Af3.6	--CCDDSECGYS-C---WPCCY# (453)
	Au3.2	G--CCS-PPCHSI-C--AAFCC# (454)
	Au3.3	--CCRPVACAMG-C---KPCC# (455)
	Au3.4	Z--CCPAVACAMG-C---EPCC# (456)
20	Em3.1	--CCS-RDC-SV-C---IPCCPYGSP^ (457)
	Ep3.1	--CCDEDECNSS-C---WPCCW# (458)
	Ep3.2	--CCDEDECSSS-C---WPCCW# (459)
	Ep3.3	--CCPAAACAMG-C---KPCC# (460)
25	Om3.1	--CCDEEECSSA-C---WPCCW# (461)
	Om3.3	--CCHLLACRFG-C---SPCCW^ (462)
	Sf3.1	--CC--PRC-SE-C---NPCC# (463)

TYPE 2

30	Pn3.2 (AA049)	-RCC--KFP-CPDS-C--KYLCC# (464)
	Fd3.2 (Z831)	-RCC--RWP-CPSI-C-GMARCCSS^ (465)
	Pu3.3 (AA405)	--CC--KLL-CYSG-C---TPCCHI^ (466)
	Eb3.1 (Z821)	--CC--EQP-CYMG-C---IPCCF^ (467)
	Eb3.2 (Z822)	--CC--AQP-CYMG-C---IPCCF^ (468)
35	Pu3.2 (AA403)	--CC--V-S-CYMG-C---IPCCF^ (469)
	Mf3.1 (Z882)	--CC--DWP-CSAG-C---YPCCFP^ (470)
	Mf3.2 (Z885)	-GCC--PPM-C-TP-C---FPCCFR^ (471)
	Ra3.2 (AA414)	RGCCAPRK-CKDRACK-PARCCGP# (472)
	Sm3.3 (AA419)	ZRCCNGRRG-CSSRWCRDHSRCC# (473)
40	Cn3.3	GRCCDVPNA-CSGRWCRDHQAQCC# (474)
	Cn3.4	ZRCCTGKKGSCSGKACKSL-KCCS# (475)

TYPE 3

45	A3.1	-MCCGEGRKCPSYFRNSQICHCC^ (476)
	A3.2 (F84)	--CCR--WPCPRQIDGEY-CGCCL# (477)
	Bu3.5	-RCCGEGLTCPRYWKNSQICACC^ (478)
	Ca3.1	--CCGPGGSCPVYFRDNFICGCC^ (479)

	Cr3.1	RKCCGKDGPCPKYFKDNFICGCC^ (480)
	E3.1	--CCS--WPCPRYSNGKLVCFCCL# (481)
	M3.2	--CCGGGSCPVYFRDNFICGCC^ (482)
	M3.3	-MCCGESAPCPSPYFRNSQICHCC^ (483)
5	M3.4	ZKCCGGGSCPVYFTDNFICGCC^ (484)
	M3.5	ZKCCGGGSCPVYFRDNFICGCC^ (485)
	S3.1	ZKCCGEGSSCPKYFKNNFICGCC^ (486)
	U001	ZKCCS-GGSCPLYFRDRLICPCC^ (487)
	U034	ZKCCGPGASCPRYFKDNFICGCC^ (488)
10	Cn3.1	-MCCGEGAPCPSPYFRNSQICHCC^ (489)

TYPE 4

15	A3.3 (F83)	ZK--CCTGK---KGCSGKACKNL-KCCS# (490)
	A3.5 (Z488)	ZK--CCTGR---KGCSGKACKNL-KCCS# (491)
	Bu3.1	VTDRCK---GKREC-GRWCRDHSRCC# (492)
	Bu3.1A	VGDRCK---GKRGC-GRWCRDHSRCC# (493)
	Bu3.2	VGERCCK---NGKRGC-GRWCRDHSRCC# (494)
20	Bu3.3	IVDRCCN-KGNGKRGC-SRWCRDHSRCC# (495)
	Bu3.4	VGLYCCRPKPNGQMMC-DRWCEKNSRCC# (496)
	Ca3.2	-RD-CCTPP---KK-CKDRQCKPQ-RCCA# (497)
	L3.1	GRD-CCTPP---RK-CKDRACKPA-RCCG# (498)
25	L3.2	ZRL-CCGFP---KS-CRSRQCKPH-RCC# (499)
	La3.2	-RD-CCTPP---KK-CKDRQCKPA-RCCG# (500)
	La3.3	RPP-CCTYD---GS-CLKESCMRK-ACC# (501)
	La3.3A	RPP-CCTYD---GS-CLKESCKRK-ACC# (502)
30	μ -GIIIA	-RD-CCTOO---KK-CKDRQCKOQ-RCCA# (503)
	μ -GIIIB	-RD-CCTOO---RK-CKDRRCKOM-KCCA# (504)
	μ -GIIIC	-RD-CCTOO---KK-CKDRRCKOL-KCCA# (505)
	μ -PIIA	ZRL-CCGFO---KS-CRSRQCKOH-RCC# (506)
	M3.1	-RD-CCTPP---KK-CKDRQCKPQ-RCCA# (507)
	Mr3.1	RGG-CCTPP---RK-CKDRACKPA-RCCGP# (508)
	Nb3.2 (F582)	ZK--CCTGK---KGCSGKACKNL-KCCS# (509)
35	Pr3.1 (Z500)	RGG-CCTPP---KK-CKDRACKPA-RCCGP# (510)
	Pr3.2 (Z501)	-RG-CCTPP---RK-CKDRACKPA-RCCGP# (511)
	R3.1	LOS-CCSLN---LRLCOVOACKRN-OCCT# (512)
	R3.2	ZQR-CCTVK---RICOVOACRSK-OCCKS^ (513)
	R3.3	RGG-CCTPP---RK-CKDRACKPA-RCCGP# (514)
40	Sm3.1	ZK--CCTGK---KGCSGKACKNL-KCCS# (515)
	T3.1	H-G-CCKGO---EG-CSSRECROQ-HCC# (516)
	T3.2 (Y088)	H-G-CCEGP---KG-CSSRECRPQ-HCC# (517)
	Wi3.1 (M548)	LPS-CCDFE---RLCVVPACIRH-QCCT# (518)

45

Type 5

Om3.2

CCKYGTLLGCTPCDC^ (519)

Om3 . 4

CCRYGWT~~C~~LGCTPCGC[^] (520)Type 6

5 S3 . 2 (F352) Z-NCCNGG-CSSKWCRDHARCC# (432)

EXAMPLE 3

Effect of Intrathecal Administration of μ -Conopeptides

10 [0087] Male C57 black mice (20-25g) are obtained from Charles River Laboratories. These mice and the animals are housed in a temperature controlled ($23^\circ \pm 3^\circ$ C) room with a 12 hour light-dark cycle with free access to food and water. All animals are euthanized in accordance with Public Health Service policies on the humane care of laboratory animals.

[0088] Intrathecal (it) drug injections are performed as described (Hylden and Wilcox, 1980). A μ -conopeptide or vehicle is administered in a volume of 5 μ l. Duration of hind-limb paralysis is assessed. This experiment reveals that injection of μ -conopeptides into the intrathecal space of C57 black mice produced a paralysis of the animal. The animals in this experiment recovered fully.

20 EXAMPLE 4

Effect of μ -Conopeptides as a Local Anesthetic

25 [0089] Male Hartley guinea pigs (retired breeders) are obtained form Charles River Laboratories. The local anesthetic test is performed essentially as described (Bulbring and Wajda, 1945). On the day prior to test day, a patch on the back of the guinea pig is denuded of hair, first by shaving with electric clippers and subsequently with depilatory cream (Nair®). Depilatory cream is applied for five minutes and removed with a warm washcloth. The guinea pigs are dried and returned to their cages. On the following day, intradermal injections (0.1 ml vols) of lidocaine, bupivacaine, a μ -conopeptide or vehicle (0.5% cyclodextran) are made into the denuded patch. The injection produced a raised wheal on the surface of the skin which is circled with a felt-tipped pen. Typically, four injections are made on the back of each guinea pig. In some cases, guinea pigs are reused following at least one week of recovery and injecting into an unused portion of the skin. The stimulus consists of mild pin pricks (not hard enough to break the skin) with a 26G needle. The response is a localized skin twitch caused by contraction

of cutaneous muscles. A unit test consisted of six uniform pin pricks, 3-5 seconds apart, within the injected area. Unit scores range from 0 (complete anesthesia) to 6 (no anesthesia). For potency experiments, the unit test is repeated at each site at five minute intervals for 30 minutes, and unit test scores summed (with 36 representing no anesthesia to 0 representing complete anesthesia. For duration experiments, unit tests are performed as described over the course of several hours to days.

[0090] μ -Conopeptides of the present invention produce a potent and long lasting local anesthetic effect in the intracutaneous wheal test in the guinea pig. As expected, bupivacaine has a slightly longer duration than lidocaine, consistent with clinical observations.

10

EXAMPLE 5

Muscle Relaxant Effect of μ -Conopeptides in Anesthetized Monkeys

[0091] μ -Conopeptides are dissolved 0.9 percent saline at a concentration of 2 mg/ml. Rhesus monkeys are anesthetized with halothane, nitrous oxide and oxygen. The maintenance concentration of halothane is 1.0%. Arterial and venous catheters are placed in the femoral vessels for drug administration and recording of the arterial pressure. Controlled ventilation is accomplished via an endotrachael tube. Twitch and tetanic contractions of the tibialis anterior muscle are elicited indirectly via the sciatic nerve. Recordings of arterial pressure electrocardiogram (lead I), heart rate, and muscle function are made simultaneously. Four to six animals received each listed compound. Four additional animals received succinylcholine chloride or d-tubocurarine chloride as controls. It is seen that the tested μ -conopeptides generally provide similar or better results than those seen for succinylcholine chloride or d-tubocurarine chloride.

25

EXAMPLE 6

In vivo Activity of μ -Conopeptides in Pain Models

[0092] The anti-pain activity of μ -conopeptides is shown in several animal models. These models include the nerve injury model (Chaplan, et al., 1997), the nociceptive response to s.c. formalin injection in rats (Codene, 1993) and an NMDA-induced persistent pain model (Liu, et al., 1997). In each of these models it is seen that the μ -conopeptides and μ -conopeptides derivatives have analgesic properties.

[0093] More specifically, this study evaluates the effect of intrathecal administration of μ -conopeptides in mice models of nociceptive and neuropathic pain. For nociceptive pain, the effect of the μ -conopeptides is studied in two different tests of inflammatory pain. The first is the formalin test, ideal because it produces a relatively short-lived, but reliable pain behavior that is readily quantified. There are two phases of pain behavior, the second of which is presumed to result largely from formalin-evoked inflammation of the hind paw. A μ -conopeptide is administered 10 minutes prior to injection of formalin. The number of flinches and/or the duration of licking produced by the injection is monitored. Since the first phase is presumed to be due to direct activation of primary afferents, and thus less dependent on long term changes in the spinal cord, μ -conopeptides are presumed to have greatest effect on the magnitude of pain behavior in the second phase.

[0094] The mechanical and thermal thresholds in animals that received an injection of complete Freund's adjuvant into the hind paw are also studied. This produces a localized inflammation including swelling of the hind paw and a profound decrease in mechanical and thermal thresholds, that are detected within 24 hours after injection. The changes in thresholds in rats that receive μ -conopeptides are compared with those of rats that receive vehicle intrathecal injections.

[0095] An important issue is whether the drugs are effective when administered after the pain model has been established, or whether they are effective only if used as a pretreatment. Clearly, the clinical need is for drugs that are effective after the pain has developed. To address this issue, animals are studied in which μ -conopeptides are administered repeatedly, after the inflammation (CFA) or nerve injury has been established. In these experiments, a μ -conopeptide is injected daily by the intrathecal (i.t.) route. The mechanical and thermal thresholds (measured, respectively, with von Frey hairs in freely moving animals and with the Hargreave's test, also in freely moving animals) are repeated for a 2 to 4 week period after the injury is induced and the changes in pain measured monitored over time.

EXAMPLE 7

Effect of μ -Conotoxins in a Pain Model

[0096] Analgesic activity of μ -conotoxins is also tested in pain models as follows.

[0097] Persistent pain (formalin test). Intrathecal (it) drug injections are performed as described by Hylden and Wilcox (1980). An μ -conopeptide or vehicle is administered in a

volume of 5 μ l. Fifteen minutes after the i.t. injection, the right hindpaw is injected with 20 μ l of 5% formalin. Animals are placed in clear plexiglass cylinders backed by mirrors to facilitate observation. Animals are closely observed for 2 minutes per 5 minute period, and the amount of time the animal spent licking the injected paw is recorded in this manner for a total of 45-50 minutes. Results are expressed as licking time in seconds per five minutes. At the end of the experiment, all animals are placed on an accelerating rotorod and the latency to first fall was recorded. μ -Conopeptides are found to be active in this model which is predictive of efficacy for treating neuropathic pain.

[0098] Acute pain (tail-flick). A μ -conopeptide or saline is administered intrathecally (i.t.) according to the method of Hylden and Wilcox (1980) in a constant volume of 5 μ l. Mice are gently wrapped in a towel with the tail exposed. At various time-points following the i.t. injection, the tail is dipped in a water bath maintained at 54° C. and the time to a vigorous tail withdrawal is recorded. If there is no withdrawal by 8 seconds, the tail is removed to avoid tissue damage.

[0099] Neuropathic pain. The partial sciatic nerve ligation model is used to assess the efficacy of μ -conopeptides in neuropathic pain. Nerve injury is produced according to the methods of Malmberg and Basbaum (1998). Animals are anesthetized with a ketamine/xylazine solution, the sciatic nerve is exposed and tightly ligated with 8-0 silk suture around 1/3 to 1/2 of the nerve. In sham-operated mice the nerve is exposed, but not ligated. Animals are allowed to recover for at least 1 week before testing is performed. On the testing day, mice are placed in plexiglass cylinders on a wire mesh frame and allowed to habituate for at least 60 minutes. Mechanical allodynia is assessed with calibrated von Frey filaments using the up-down method as described by Chaplan et al. (1994), and the 50% withdrawal threshold is calculated. Animals that did not respond to any of the filaments in the series are assigned a maximal value of 3.6 grams, which is the filament that typically lifted the hindlimb without bending, and corresponds to approximately 1/10 the animal's body weight.

[0100] The data obtained demonstrate that μ -conopeptides have potent analgesic properties in three commonly used models of pain: acute, persistent/inflammatory and neuropathic pain models.

EXAMPLE 8

Activity of μ -Conopeptide S3.2 on Neuronal Sodium Channels

[0101] μ -Conopeptide S3.2 was tested for activity on sodium channels as follows. S3.2 was administered to mice by intracerbroventricular (ICV) injection. Administration of S3.2 in this manner caused mice to show a spectrum of activity that is characteristic of all sodium channel blockers, including rapid loss of righting reflex, coma-like inactivity and spastic uncontrolled limb movement. Following intrathecal (it) administration to mice, S3.2 causes rapid hindlimb paralysis that spreads to include the entire body over a course of 10-20 minutes followed by death, presumably due to respiratory paralysis. However, unlike classic μ -conopeptides, S3.2 has no significant activity following intravenous administration (iv) to mice. Classic μ -conopeptides, such as GIIIA and PIIIA, cause rapid paralysis and death following iv administration, indicating their activity at skeletal muscle sodium channels. To confirm the selectivity of S3.2, 80 nmol was administered iv to rats. The effect of S3.2 was measured on skeletal muscle contraction, blood pressure and heart rate. S3.2 was found to have no effect on any of these parameters. Controls were performed using classical μ -conopeptides, including Sm3.1, Sm3.3 and Bu3.1 described herein, also administered iv at 80 nmol. These control peptides caused a dramatic decrease in skeletal muscle contractility, as well as a significant drop in systemic blood pressure. Thus, μ -conopeptide S3.2 surprisingly is selective for neuronal sodium channels. The most obvious difference between the S3.2 sequence and the sequences of these other peptides is a shortened first loop (the first loop between cysteine residues) which lacks a charged amino acid.

[0102] It will be appreciated that the methods and compositions of the instant invention can be incorporated in the form of a variety of embodiments, only a few of which are disclosed herein. It will be apparent to the artisan that other embodiments exist and do not depart from the spirit of the invention. Thus, the described embodiments are illustrative and should not be construed as restrictive.

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